Chronic Effects of 3,4-Methylenedioxymethamphetamine on Social and Non-Social Cognition

Thesis (cumulative thesis)

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Abstract

Cognitive deficits in abstinent MDMA users were reported in various domains. The findings regarding attention, working memory, and executive function deficits are inconclusive, and were criticized for being induced by the co-use of other drugs.

Moreover, social cognition and social decision-making have rarely been investigated in chronic MDMA users but in animals, long-lasting depletions of oxytocin (OXT) have been reported after chronic MDMA treatment implicating a potential impact on social cognition and behavior.

The present thesis aims to eliminate the issue of unreliable self-reported drug use by investigating social and non-social cognition and social decision-making in objectively verified pure and polydrug MDMA users. Additionally, plasma OXT levels of a subsample were investigated.

Verified pure MDMA users showed large deficits in declarative memory, while MDMA users with a co-use of stimulants shoved additional and stronger impairments in working memory and executive functions. Main MDMA users showed higher cognitive empathy but did not differ from controls in emotional empathy. Moreover, MDMA users acted less self-serving. However, higher hair MDMA values went along with a decrease in cognitive empathy. OXT plasma levels did not significantly differ between the two groups.

Overall, our results suggest that even pure chronic MDMA users display strong impairments in declarative memory and that the broad cognitive impairments in polydrug MDMA users are driven by stimulant co-use. Additionally, they suggest that people with high cognitive empathy might be more prone to use MDMA chronically, which likely leads to a decrease in cognitive empathy.

Zusammenfassung

Bei chronischen MDMA Konsumenten wurden eine Vielzahl an kognitiven Defiziten berichtet. Die Befundlage bezüglich Arbeitsgedächtnis, Aufmerksamkeit und exekutiven Funktionen scheint unschlüssig, wobei vor allem die Erfassung des Drogenkonsums mittels Befragung häufig kritisiert wurde.

Die soziale Kognition und das soziale Entscheidungsverhalten wurden zudem in chronischen MDMA Konsumenten erst spärlich untersucht. In Tierversuchen konnte nach wiederholter MDMA Gabe eine langfristige Senkung des Oxytocinspiegels beobachtet werden, was einen Einfluss auf das Sozialverhalten nahelegt.

Durch die objektive Messung des Drogenkonsums mittels Haaranalysen wird im Rahmen dieser Arbeit das Problem des selbstberichteten Drogenkonsums zu beseitigen versucht. Dazu wird die soziale und nicht-soziale Kognition, das soziale Entscheidungsverhalten sowie Blutplasmaoxytocinspiegel von reinen und polytoxischen MDMA Konsumenten erhoben. Es zeigten sich bereits bei reinen MDMA Konsumenten erhebliche Einschränkungen des deklarativen Gedächtnisses. Zusätzlich zeigten MDMA Konsumenten eine höhere kognitive Empathie, wobei sie sich in der emotionalen Empathie nicht von den Kontrollen unterschieden. Dazu verhielten sie sich prosozialer als die Kontrollgruppe. Höhere MDMA Haarwerte gingen mit einer Abnahme der kognitiven Empathie einher. Oxytocinspiegel unterschieden sich nicht signifikant zwischen den Gruppen.

Zusammen genommen zeigen diese Resultate, dass bereits reine MDMA Konsumenten starke Einbussen im deklarativen Gedächtnis zeigen und dass breitgefächerte und starke kognitive Beeinträchtigungen bei polytoxischen MDMA Konsumenten wahrscheinlich durch den Co-Konsum von Stimulanzien induziert sind. Personen mit hoher kognitiver Empathie und prosozialem Verhalten neigen möglicherweise zu MDMA Konsum. Dieser könnte aber chronisch ausgeprägt zu Einbussen in der kognitiven Empathie führen.

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Content

1 General Introduction

1.1 Outline

The substance 3,4-methylenedioxymethamphetamine (MDMA), better known under its street name Ecstasy (Gouzoulis-Mayfrank and Daumann, 2006), was first researched on laboratory animals in 1953 (Hardman et al., 1973), but it was not until 1978 when the first publication of its psychopharmacological effects in humans was published (Shulgin and Nichols, 1978), 66 years after its first synthesis in 1912 (Shulgin, 1986; Benzenhofer and Passie, 2010). In the mid-1980s, the recreational use of MDMA commenced, which entailed empirical studies investigating physiological, psychobiological as well as psychiatric effects of the drug (Shulgin, 1986; Peroutka et al., 1988; Peroutka, 1989; McCann and Ricaurte, 1991; Parrott et al., 2017). Hereby, McCann and Ricaurte (1991) reported retrospective memory deficits in two abstinent MDMA users for the first time. In subsequent years, evidence for memory deficits, which were often measured via delayed recall tasks, accumulated (Laws and Kokkalis, 2007; Parrott et al., 2017). Up to now, cognitive deficits in abstinent MDMA users were reported in various other cognitive domains also, including attention, working memory, and executive functions (Kalechstein et al., 2007). However, the findings regarding deficits in these four domains are inconclusive on the one hand, and were criticized for possibly being confounded by the co-consumption of drugs other than MDMA itself on the other hand (Cole, 2014). Therefore, the aim of our first study was to partial out the cognitive deficits possibly caused by long-term MDMA consumption and to delimit them from those deficits possibly induced by a polydrug use pattern.

Social cognition is an important predictor for the development and course of drug addiction because deficits in social cognition are associated with social isolation, depression, and aggression, which support the maintenance of drug use (Homer et al., 2008; Volkow et al., 2011). Despite the importance of social cognition for the topic of drug use in general, social cognition and social decision making, was mainly investigated in the context of acute effects of MDMA (Hysek et al., 2012; Hysek et al., 2014b; Hysek et al., 2014a; Schmid et al., 2014; Kuypers et al., 2017), while long-term effects were less often researched (Reay et al., 2006). This is no surprise, given that the main subjective effects and the main reason for consumption are increased prosocial feelings (Morgan et al., 2013). These prosocial effects of MDMA have been proposed to be mediated by an increased oxytocin release (Thompson et al., 2007). Given that chronic administration of MDMA leads to a long-lasting depletion of oxytocin in animal models (van Nieuwenhuijzen et al., 2010), it was predicted that MDMA has a detrimental effect on the oxytocin system and consequently on social cognition in human users, which is what we wanted to investigate in our second study.

In sum, the present thesis has two main goals. (1) To partial out the main cognitive long-term effects of chronic MDMA consumption from the effects of polydrug co-use on the one hand (Study 1), and to describe the long-term effects of chronic MDMA consumption on social cognitive performance and social decision making on the other hand (Study 2).

1.2 General facts about MDMA

MDMA was first synthesized by the chemical company Merck in Germany in 1912 and later patented in 1914 (Siegel, 1986). Its primary effects are blocking and reversing the serotonin (5-HT) transporter, therefore acting as an indirect antagonist on the 5-HT system. Via transporter-mediated exchange, 5-HT is released through the 5-HT transporter, which leads to a significant increase in synaptically available 5-HT, especially because MDMA also increases the amount of available 5-HT by inducing 5-HT efflux from vesicles (Rudnick and Wall, 1992; Kalant, 2001). MDMA also acts on dopaminergic and noradrenergic neurotransmitter systems, but the main psychological effects of MDMA were shown to depend on 5-HT release, whereas stimulant-like euphoric effects are a consequence of dopamine receptor stimulation (Liechti and Vollenweider, 2001). Typically, MDMA is consumed orally while a recreational dose contains 70 to 120mg of MDMA (Parrott, 2004). MDMA leads to psychological effects including euphoria and well-being together with increased sociability, feelings of closeness with others, elevated self-confidence, and reduced inhibition (Vollenweider et al., 1998; Bedi et al., 2010). These acute effects of MDMA – which last for about three to five hours (Kolbrich et al., 2008) – were described as entactogenic and empathogenic, which is why MDMA has been labeled a *entactogens* and *empathogen* in contrast to stimulants or hallucinogens that differ from MDMA in their psychoactive profile (Nichols, 1986; Bedi et al., 2009). After oral consumption, MDMA is detectable in the blood after 30 minutes, while the highest plasma concentrations occur after one to three hours after consumption. The elimination half-life of typical recreational doses of MDMA is about eight to nine hours (Mas et al., 1999).

1.3 Epidemiology of MDMA use

The United Nations Office on Drugs and Crime (2016) estimated that worldwide, 19.4 million people consumed MDMA in 2014. This number increased in 2015 to 21.65 million past year users (United Nations Office on Drugs and Crime, 2017) and shows, that MDMA is one of the most used illicit drugs worldwide.

Also in Europe, MDMA was the third most consumed illegal drug (after cannabis and cocaine) with 14 million last year users between 15 and 64 years of age, which equals 4.2% of the people in this age range (European Monitoring Centre for Drugs and Drug Addiction, 2017). For the age range of 15 to 34 years, 2.3 million young adults consumed MDMA in the past year, which equals 1.8% of this age group.

In Switzerland, the Federal Office of Public Health (Gmel et al., 2016) estimated that people aged over 15 have a last-year prevalence of 0.3%, while the last-year prevalence is highest for adults aged 20 to 24 years with 1.5%.

Finally, applying wastewater analyses – an innovative approach to measure drug use on a community level – Been et al. (2016) revealed that in Zurich, the measured load of MDMA per 1000 inhabitants is highest and lowest in the city of Lugano.

1.4 MDMA use and cognition

Broadly speaking, brain regions associated with drug addiction extend over those responsible for cognitive functions (Gould, 2010). In the following chapter, the connection between MDMA-induced neurological alterations and cognitive functions, especially declarative memory function, will be outlined.

As described above, the consumption of MDMA leads to an acute immense neuronal release of 5-HT but also of noradrenalin (Rothman et al., 2001; Cadet et al., 2007). Consequently, the neurotoxic effects of MDMA primarily involve the 5-HT system and in rats and even in non-human primates, detrimental effects of large doses of MDMA on 5-HT neurons were reported already in the 1980s (Schmidt et al., 1986; Ricaurte et al., 1988). In general, evidence for the neurodegeneration hypothesis of MDMA from animal studies can be summarized as follows. After single or multiple administrations of large doses of MDMA, forebrain levels of 5-HT and 5-hydoxyindoleacetic acid (main 5-HT metabolite) decrease, and synaptosomal 5-HT uptake, and radiolabeled 5-HT transporter (SERT) binding is reduced 1 to 2 weeks after the last drug administration (Biezonski and Meyer, 2011), while dopaminergic and noradrenergic neurotransmitter systems remain undamaged (Insel et al., 1989; Biezonski and Meyer, 2011).

In humans, as mentioned before, the first cognitive impairments in the context of MDMA use were reported by McCann and Ricaurte (1991) and encompassed self-reported retrospective memory deficits (Parrott et al., 2017). Consequently, declarative memory deficits were the first deficits to be associated with MDMA use (Krystal et al., 1992). In subsequent years, evidence for a relationship between MDMA consumption and memory deficits were delivered in two ways (Kuypers et al., 2016). (1) Placebo-controlled studies have shown that 75mg of MDMA acutely leads to a significant lower recall performance on recall tests (immediate as well as delayed recall) 1.5 hours after intake (Kuypers and Ramaekers, 2005; Kuypers et al., 2013; de Sousa Fernandes Perna et al., 2014). Studies in which MDMA was given to participants also revealed that after 25.5 hours (after MDMA administration), the subject's memory performance was equal to the placebo control group's showing that a single dose of MDMA does not lead to permanent verbal memory deficits (Kuypers and Ramaekers, 2005). (2) The second source of evidence for memory deficits in the context of MDMA consumption are retrospective studies, which investigated if these acute effects can become chronic after the substance

was used regularly. In a huge systematical review, Rogers et al. (2009) conclude that immediate and delayed verbal memory deficits are associated with MDMA use. Similarly, Kalechstein et al. (2007) found strong effects for the neurocognitive domain of verbal learning and memory in their meta-analytic review, while non-verbal learning, attention, and executive function only reached small to moderate effect sizes.

Evidence for a linkage between MDMA consumption and cognitive impairments not only comes from observational investigations (Quednow et al., 2006), but also from a linkage on the neurological/neuroanatomical level. MDMA induced decreases in SERT levels were found in a variety of brain regions, including the dorsolateral prefrontal cortex (DLPFC) (Roberts et al., 2016), which is responsible for encoding, recall, and recognition of memory content (Ranganath et al., 2003).

Reviews and the reviewed retrospective studies themselves were repeatedly criticized because of methodological concerns (Curran, 2000; Cole, 2014). The main criticism are polydrug co-use, possible impurity of ecstasy tablets, and that drug use patterns are usually self-reported by the study participants (Kuypers et al., 2016). The fact that MDMA consumption is often measured via self-reports (drug interviews) together with the fact that MDMA users tend to co-use other drugs (Schifano et al., 1998) raises concern about the validity of past findings, because consequently, cross-sectional studies cannot conclusively attribute performance differences between MDMA users and drug-naïve controls to MDMA use alone (Curran, 2000). Additionally drug users might be motivated to give a biased self-report or they might over- or underestimate their drug use because of memory alterations (Magura and Kang, 1996; Quednow et al., 2006).

To bypass this problem, we objectively quantified our participants' drug use via toxicological hair testing. This allowed us to distinguish between relatively pure MDMA users, whose hair analyses did not reveal co-consumption of stimulants, and so called polydrug MDMA users, which mainly consumed stimulants additionally.

In sum, the literature has repeatedly shown declarative memory impairments in chronic MDMA users (Parrott, 2001; Kalechstein et al., 2007), while attention, working memory, and executive functions were reported to be impaired less consistently and with lower effect sizes. Because we suspected that the reason for inconsistencies regarding deficits in attention, working memory, and executive functions might lie in the methodological issues presented above, we aimed to control polydrug co-use by hair analyses in our first study.

1.5 MDMA use and social cognition

Social cognition refers to different mental operations which underlie everyday social interactions (Fiske and Taylor, 1991). This concept includes the recognition of emotions, mental perspective taking also referred to as Theory of Mind (ToM), and empathy (Davis, 1983; Blair, 2005; Dziobek et al., 2008), while the two concepts of ToM and empathy partially overlap. This is because empathy is conceptualized as having two components, the cognitive and the emotional empathy. Cognitive empathy encompasses the ability to decode and understand emotions and mental states (ToM) of others (Baron-Cohen and Wheelwright, 2004; Blair, 2005), and emotional empathy describes a person's emotional response to another's emotional state (Blair, 2005; Dziobek et al., 2008). The acute effects of MDMA on social cognition are of interest, because MDMA users reported to use the substance with the intention of initiating empathic feelings and enhance sociability (Morgan et al., 2013; Schmid et al., 2014). A number of studies have investigated subjective experiences of MDMA (Bedi et al., 2010) and found, among others, increases in perceived empathy and self-related friendliness, extroversion, sociability, amicability, gregariousness and closeness to others (Vollenweider et al., 1999; Tancer and Johanson, 2007; Kolbrich et al., 2008; Dumont et al., 2009).

In animals, the acute effects of MDMA on social behavior, which is often measured with the social interaction test, have been researched extensively. Hereby, rodents are exposed to unfamiliar conspecifics and behaviors like adjacent lying and friendly following are measured (Kamilar-Britt and Bedi, 2015). Both measures were consistently reported to be increased in rats after the administration of 5mg/kg to 15mg/kg and 2.5mg/kg to 10mg/kg of MDMA respectively (Ando et al., 2006; Thompson et al., 2009; Kamilar-Britt and Bedi, 2015). Together with decreased aggression and elevated social reward, literature consistently suggests a prosocial effect profile of MDMA in rodents (Kamilar-Britt and Bedi, 2015). In humans, acute effects on social cognition have been researched recently, while the literature mostly focusses on effects on cognitive and emotional empathy (Hysek et al., 2012; Hysek et al., 2014b; Schmid et al., 2014).

Regarding cognitive empathy, acute MDMA intake has repeatedly been shown to reduce the identification of negative emotional stimuli such as fear or anger in others (Bedi et al., 2010; Hysek et al., 2012; Hysek et al., 2014b; Hysek et al., 2014a; Kirkpatrick et al., 2014) and one study additionally found an increased recognition of friendliness in others, a positive emotional stimuli (Hysek et al., 2012). Thus, MDMA may – based on the increased recognition of positive emotional stimuli and the decreased recognition of negative emotional stimuli but also because of the induced prosocial states – facilitate social behavior (Kirkpatrick et al., 2014) and social decision making.

In summary, research on empathy performance suggests that acute MDMA intake decreases cognitive empathy but enhances emotional empathy (Kamilar-Britt and Bedi, 2015). Interestingly, these acute prosocial effects of MDMA have been linked to the release of central oxytocin (OXT), which is a peptide that plays a crucial role in social bonding in mammalians (Bos et al., 2012). Several studies

have found dose-dependent increases in blood plasma OXT levels after MDMA administration (Wolff et al., 2006; Dumont et al., 2009; Hysek et al., 2012; Schmid et al., 2014) which correlated with increased feelings of sociability (Dumont et al., 2009). Given that a former animal study documented lasting depletion of brain OXT after long-term MDMA administration (van Nieuwenhuijzen et al., 2010), we investigated social cognition and social decision making together with blood plasma OXT levels in abstinent, long-term MDMA users. For the same reasons as already mentioned in the chapter before – 1) MDMA users often co-use other drugs (Schifano et al., 1998; Curran, 2000), 2) research has been criticized for unreliably measuring past drug use through drug interviews (Cole, 2014), and 3) drug users might be motivated to give a biased self-report or simply over- or underestimate their own consumption because of consistently shown memory alterations (Magura and Kang, 1996; Quednow et al., 2006) – we objectively determined drug use through quantitative hair analyses.

1.6 Research objectives

Altogether, evidence accumulated for an association between the repeated use of MDMA and deficits in the cognitive functions of attention, working memory, executive functions and declarative memory. However, it is unclear what part of these impairments may be due to polydrug and especially stimulant co-consumption. For social cognition and social decision-making, the performance of long-term MDMA users has not been described to date. Therefore, this thesis is designed to help clarify the role of chronic, long-term MDMA use and polydrug co-use with regard to cognitive functioning and to further assess social cognition, social decision making and blood plasma OXT levels in main chronic users of MDMA.

In order to examine these issues, we conducted two studies (chapter 2 and 3). In the first study (chapter 2), we investigated a cross-sectional sample of 26 pure MDMA users, 25 polydrug MDMA users and 56 MDMA- and drug-naïve healthy controls with a comprehensive neuropsychological test battery. In the second study (chapter 3), we analyzed an overlapping study sample consisting of all the pure MDMA users from the first study (26) and 12 polydrug MDMA users, for which MDMA was the first drug of choice.

As described before, the lack of control for polydrug consumption is a major issue in MDMA research. Accordingly, data from these studies that objectively measure drug use via toxicological hair analyses will enable us to entangle cognitive impairments possibly induced by chronic MDMA consumption from those induced by polydrug co-use in study 1. In study 2, the objective hair drug values will enable us to precisely characterize social cognition and social decision making of long-term MDMA users in contrast to MDMA- and drug-naïve controls.

1.7 Data collection

This thesis was part of the Zurich Cocaine Cognition Study ($ZuCo^2St$) which started in 2010. The project was supervised by Prof. Dr. rer. nat. Boris Quednow, head of the Division of Experimental and Clinical Pharmacopsychology at the University Hospital of Psychiatry in Zurich and funded by the Swiss National Science Foundation (SNSF, grants PP00P1-123516/1 and PP00P1-146326/1). The $ZuCo^2St$ was designed to assess the long-term consequences of cocaine use on different measures of social and non-social cognition, impulsivity, and decision-making with the possibility to extend the recruitment to participants consuming other drugs than cocaine. To recruit the participants for this thesis, a new recruitment phase was started in August 2014, which lasted until August 2015. The data were collected in Zurich and participants were recruited via online media and flyer advertisements as well as via word of mouth. In total, 53 long-term MDMA users and 56 drug and MDMA-naïve controls were recruited. All subjects were aged between 18 and 60 years and had sufficient German language skills. As a special feature of the studies constituting this thesis, the group allocation was not only based on the participants self-reported drug consumption, but on objective hair analyses. These hair analyses enabled us to quantify the participant's use of 17 substances and metabolites for up to the last 6 months prior to testing. In the first study – where our focus was on the cogntive difference between pure and polydrug MDMA users – we compared 26 pure MDMA users with 25 polydrug MDMA users (and 56 controls) after two participants were excluded because of missing/deficient hair samples. In the second study – where we focused on main MDMA users that consume MDMA as their main drug of choice – we excluded an addition 13 MDMA users because their hair analyses implied a preference for stimulants over MDMA in the past half year. We therefore compared 38 main MDMA users with 56 drug and MDMA-naïve controls in the second study investigating social cognition and interaction.

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2 Discrete memory impairments in largely pure chronic users of MDMA

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Personal Contribution

BBQ designed this study and all authors contributed to its planning, analysis strategy and interpretation of the data. BBQ, MV, MF, KS, and MDW were responsible for the neuropsychological assessment of the study participants. Qualitative urine and hair testing was performed by MRB and TK. Statistical analyses were conducted by MDW under the supervision of BBQ. All authors had access to the data and the statistical outputs and critically revised the article after MDW had drafted it. All authors approved the final manuscript.

2.1 Abstract

Background: Chronic use of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") has repeatedly been associated with deficits in working memory, declarative memory, and executive functions. However, previous findings regarding working memory and executive function are inconclusive yet, as in most studies concomitant stimulant use, which is known to affect these functions, was not adequately controlled for.

Methods: Therefore, we compared the cognitive performance of 26 stimulant-free and largely pure (primary) MDMA users, 25 stimulant-using polydrug MDMA users, and 56 MDMA/stimulant-naïve controls by applying a comprehensive neuropsychological test battery. Neuropsychological tests were grouped into four cognitive domains. Recent drug use was objectively quantified by 6-month hair analyses on 17 substances and metabolites.

Results: Considerably lower mean hair concentrations of stimulants (amphetamine, methamphetamine, methylphenidate, cocaine), opioids (morphine, methadone, codeine), and hallucinogens (ketamine, 2C-B) were detected in primary compared to polydrug users, while both user groups did not differ in their MDMA hair concentration. Cohen's *d* effect sizes for both comparisons, i.e., primary MDMA users vs. controls and polydrug MDMA users vs. controls, were highest for declarative memory ($d_{primary}$=.90, d_{polydrug}=1.21), followed by working memory ($d_{primary}$=.52, d_{polydrug}=.96), executive functions ($d_{primary}$=.46, d_{polydrug}=.86), and attention ($d_{primary}$=.23, d_{polydrug}=.70).

Conclusion: Primary MDMA users showed strong and relatively discrete declarative memory impairments, whereas MDMA polydrug users displayed broad and unspecific cognitive impairments. Consequently, even largely pure chronic MDMA use is associated with decreased performance in declarative memory, while additional deficits in working memory and executive functions displayed by polydrug MDMA users are likely driven by stimulant co-use.

2.2 Introduction

With a global estimate of 19.4 million users in 2014 (United Nations Office on Drugs and Crime, 2016) 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") remains one of the most used illicit drugs worldwide. MDMA is a synthetic substituted amphetamine derivate that blocks and reverses the monoamine transporters leading to a rapid release of monoamines, especially of serotonin (5-HT) but also of noradrenalin and dopamine (Rudnick and Wall, 1992; Kalant, 2001). In rodents and in non-human primates, research found evidence for long-term loss of 5-HT nerve terminals (Commins et al., 1987; Ricaurte et al., 1988; Hatzidimitriou et al., 1999). In humans, MDMA-related reductions of 5-HT transporters in different regions of the basal ganglia and the neocortex have been reported analogously (for review see Roberts et al., 2016a). Over the past three decades, the behavioral effects of MDMA use have been investigated extensively, and a broad range of cognitive dysfunctions has been reported in long-term MDMA users (Parrott, 2013).

While declarative memory impairments have been consistently shown in MDMA users with moderate to large effect sizes (for review see Kalechstein et al., 2007; Parrott, 2013), other cognitive domains yielded inconclusive results. The meta-analysis from Laws and Kokkalis (2007) found a medium effect size (d=0.63) for working memory (short-term memory) deficits in recreational MDMA users, but also reported that impairments are likely driven by verbal working memory deficits, whereas visual working memory may be primarily affected by cannabis use. On the other hand, working memory deficits found in the often applied (immediate) prose recall task (Morgan, 1999), which measures verbal working (immediate recall) and declarative memory (delayed recall), could not be replicated by all investigators (e.g., Thomasius et al., 2003; 2006). Moreover, a meta-regression over 12 comparisons revealed that differences in immediate prose recall between MDMA users (or ex-MDMA users) and controls are partially ascribable to the group's unequal intelligence status (Rogers et al., 2009). For delayed recall tasks (declarative memory), the same bias was found, but, in contrast to working memory performance, differences between MDMA users and controls remained significant after controlling for intelligence status (Rogers et al., 2009).

Regarding potential attention deficits in MDMA users, results seem to differ between studies investigating basic or higher order attention: Some studies examining basic attention or vigilance reported no impairments (Rodgers, 2000; e.g., Back-Madruga et al., 2003; Parrott, 2013), in contrast to studies investigating higher order sustained attention that found strong impairments (McCann et al., 1999; Fox et al., 2001). However, in a meta-analytic review, Kalechstein (2007) reported only small to moderate effect sizes for attention/concentration deficits in MDMA users compared to matched controls. For executive functions, a recent meta-analysis by Roberts et al. (2016b) investigated four components of executive functions: inhibition, switching, updating (Miyake et al., 2000), and access (Fisk and Sharp, 2004) and found that – compared to non-MDMA polydrug using controls – polydrug MDMA users display significant alterations with a small effect size in all functions with exception of

the unaffected inhibition component. However, the authors state that they cannot rule out the possibility that concomitant drug use contributed to the deficits found in executive functioning of the polydrug MDMA users.

Inconsistencies and interpretation difficulties within findings for cognitive deficits in long-term MDMA users – especially regarding working memory and attention - are apparent and may be partially explained by different factors limiting the interpretation of results. Perhaps the most serious disadvantages of human MDMA research are that drug consumption is mostly measured via self-reports (drug interviews) and that MDMA users often use other drugs (Schifano et al., 1998). Consequently, the interpretation of performance differences between MDMA users and controls in cross-sectional studies cannot be attributed solely to MDMA use (Curran, 2000). This is evident in experiments comparing polydrug MDMA users with drug-naïve controls, as possible long-term effects cannot be distinguished from the effects of other drugs. Also, in experiments with a non-MDMA polydrug control group, possible interaction effects between MDMA and other drugs may mask the pure effects of MDMA. Lastly, studies investigating non-polydrug MDMA users that do not quantitatively objectify (e.g., by toxicological hair testing) drug use remain unaware of the truth-value of the reported drug use patterns assessed with drug interviews. Because drug users might have different motivations to give a biased self-report or simply over- or underestimate their own consumption because of consistently shown memory alterations, we objectively quantified drug use through hair analyses in the present study.

To our knowledge, no study has investigated cognitive alterations in a sample of objectively confirmed pure MDMA users so far. Thus, we compared largely pure (in the following also called "primary" MDMA users) and polydrug MDMA users with drug-naïve healthy controls on well-established cognitive tasks. Drug use during the last months was objectively determined by quantitative hair analyses for all participants. We hypothesized that largely pure MDMA users still show disturbed declarative memory functions with a strong effect size, whereas other cognitive domains are only slightly or moderately impaired. In contrast, we expect stimulant-using polydrug MDMA users to show additional impairments in working memory, executive functions and attention given that these cognitive domains have been shown to be affected by cocaine (Jovanovski et al., 2005; Vonmoos et al., 2013; Vonmoos et al., 2014), amphetamine (Lundqvist, 2005), and methamphetamine use (Scott et al., 2007).

2.3 Method

2.3.1 Participants

Within the context of the Zurich Cocaine Cognition Study (ZuCo^{2}St), which has started in 2010 (Vonmoos et al., 2013; Quednow, 2016), we recruited 53 long-term MDMA users and 56 drug-naïve, healthy controls by means of flyer and online media advertisements. Prior to testing, candidates underwent a brief telephone screening to assess their study eligibility. All subjects had to be aged between 18 and 60 years and had to have sufficient German language skills. Based on the results of the hair analyses (see below), 25 MDMA users were classified as polydrug MDMA users, 26 were classified as primary MDMA users and 2 MDMA users were excluded because of deficient/missing hair samples. Participants were categorized as primary MDMA users only if their hair analyses revealed MDMA consumption and the hair cocaine and amphetamine concentrations – the most common co-used drugs in our sample – did not exceed the cut-off values of 500pg/mg or 200pg/mg respectively (Cooper et al., 2012). Based on these cut-off values, we consequently classified participants as polydrug MDMA users if their amphetamine or cocaine hair concentrations exceeded these values and MDMA metabolites were detected (see Table 1 and Supplementary Table S1). This enabled us to compare 26 stimulant-free, primary MDMA users with 25 stimulant-using polydrug MDMA users, and 56 drug-naïve healthy controls. The groups were matched for age, sex, verbal intelligence, years of education, depression scores, and cannabis consumption during the past half year (Table 2).

The general exclusion criteria encompassed current or previous neurological disorders or head injuries, any clinically significant medical disease, a family history of schizophrenia or bipolar disorder, the prescription of drugs affecting the central nervous system, and a lifetime history of opioid use. Additionally, all participants who reported daily cannabis consumption were excluded. Controls were also excluded if they fulfilled the diagnostic criteria for any Axis-I *DSM-IV* psychiatric disorder including any form of addiction (except nicotine), or if they reported current or previous regular illegal drug use (except cannabis). Exclusion criteria for the MDMA groups were any acute or previous Axis-I *DSM-IV* adult psychiatric disorders with the exception of MDMA, alcohol, and nicotine misuse and a history of depression (acute major depression was excluded). Inclusion criteria for the MDMA group were MDMA use of at least 100 occasions or weekly consumption during the last year, and a current abstinence period of less than 6 months.

All participants were asked to abstain from illegal substances for at least three days and from alcohol for at least 24h prior to testing. Drug urine screenings controlled for compliance (see below). The Cantonal Ethics Committee of Zurich has approved the study, and all participants gave written informed consent. The participants were compensated for their participation with 180 Swiss Francs.

2.3.2 Clinical assessment

Trained psychologists conducted the Structured Clinical Interview for Axis-I *DSM-IV* disorders in order to exclude participants with an Axis-I *DSM-IV* psychiatric disorder. Depressive symptoms were assessed with the Beck Depression Inventory (BDI) (Beck et al., 1961). Severity of ADHD symptoms was evaluated with the ADHD self-rating scale (ADHD-SR) corresponding to *DSM-IV* criteria (Rosler et al., 2004). Premorbid verbal intelligence was estimated with a German vocabulary test (*Mehrfachwahl-Wortschatz-Intelligenztest*) (Lehrl et al., 1995).

2.3.3 Drug use assessment

Self-reported drug use was assessed with the Interview for Psychotropic Drug Consumption (Quednow et al., 2004). In addition, to objectively quantify the participant's drug use, hair samples were taken from the posterior vertex region of the head in order to determine the concentration of 17 common drugs and their metabolites by liquid chromatography-tandem mass spectroscopy (Cooper et al., 2012). To exclude intoxication at testing, urine drug screenings were employed by semi-quantitative enzyme multiplied immunoassay (see Supplementary Methods S1 for technical details).

2.3.4 Assessment of cognitive performance

Cognitive performance was assessed with four tests from the Cambridge Neuropsychological Test Automated Battery (Strauss et al., 2006): Rapid Visual Information Processing, Spatial Working Memory, Intra/Extra-Dimensional Set Shifting, and Paired Associates Learning. Furthermore, a German version of the Rey Auditory Verbal Learning Test (Helmstaedter et al., 2001) and the Letter Number Sequencing Task were administered (Wechsler, 1997). As previously published (Vonmoos et al., 2013; 2014), 15 predefined test parameters were z-transformed based on means and standard deviations of the control group and combined into four cognitive domains (Goldstein et al., 2004; Jovanovski et al., 2005; Pace-Schott et al., 2008; Woicik et al., 2009; Vonmoos et al., 2013): attention, working memory, declarative memory, and executive functions (see Supplementary Methods S3 for further details).).

2.3.5 Statistical analysis

We performed the statistical analyses with SPSS 22.0 for Windows. Demographic and drug use data for all groups were analyzed with Pearson's chi-square test and analyses of variance (ANOVA). To investigate group differences over all groups in cognitive parameters, we performed a multiple linear regression with the dummy coded (zero, 1) group variables as independent variables. To compare

controls to the MDMA user groups, controls were chosen as the reference group, whereas for the comparison of the two MDMA using groups, polydrug MDMA users were coded 0 (Fig. 1 and Table 3). To be able to assess the practical significance of cognitive performance differences between controls and the MDMA using groups, Cohen's *d* effect sizes were calculated based on the means and pooled standard deviations (SD) of the two groups being compared (Cohen, 1988). Finally, we conducted multiple regression analyses (forced entry) to investigate the relationship between preselected predictors (age, sex, verbal IQ, grouping variables, BDI score and ADHD-SR score) and declarative memory performance. Further, multiple regression analyses were conducted over the MDMA users only to investigate possible factors influencing declarative memory performance in MDMA users; Model 1 estimated memory performance through drug use patterns covering the past six months (hair analyses and drug use per week) and in Model 2, estimations were based on drug use variables describing the duration of use or cumulative lifetime dose. Based on an à priori power analysis with G*Power 3.1.9.2 (Faul et al., 2007) (Linear multiple regression: Fixed model, single regression coefficient, f^2=0.15, α= 0.05, two predictors), this study has an alpha-error probability of 5% and a power of over 85%.

2.4 Results

2.4.1 Demographic characteristics and drug use

For demographic parameters, the groups did not differ significantly in age, verbal IQ, years of education, sex distribution, and depression scores (Table 2). For age, the middle 50% of all participants were aged between 22 and 29 years, while the youngest participant was 18 and the oldest 47 years old. However, both MDMA groups differed from controls with regard to their ADHD-SR scores. For objective drug-use measures, polydrug and primary MDMA users had significantly higher MDMA hair drug concentrations than controls but did not differ from each other. Importantly, only polydrug MDMA users differed from controls in amphetamine, cocaine and ketamine hair concentrations, whereas primary MDMA users only showed minimal exposure to these drugs (for detailed hair analyses of all MDMA users see Table 1). For cannabis, amphetamine, and cocaine, primary MDMA users showed no significant differences regarding positive urine tests compared to controls, while the polydrug MDMA user group contained three cocaine-positive urine analyses. Primary MDMA users did not differ significantly from controls in any tobacco, alcohol, and cannabis measure, while polydrug MDMA users reported stronger current smoking and drinking habits.

Table 1: Hair analyses parameters for all groups.

	Controls (n=56)	Primary MDMA (n=26)	Polydrug MDMA (n=25)
MDMA			
Hair analysis pg/mgd	0.00 (0.00)	3414 (9184)	4894 (5398)
Min / max hair value	0.00 / 0.00	32 / 48000	134 / 17500
N > 0	0	26	25
MDEA			
Hair analysis pg/mgd	0.00 (0.00)	7.5 (23.64)	12.96 (31.54)
Min / max hair value	0.00 / 0.00	0 / 114	0 / 145
N > 0	0	4	6
MDA			
Hair analysis pg/mgd	0.00 (0.00)	90.15 (79.68)	187.96 (247.2)
Min / max hair value	0.00 / 0.00	0 / 331	0 / 1088
N > 0	0	25	23
Amphetamine			
Hair analysis pg/mg	0.00 (0.00)	38.5 (63.8)	801.0 (1804)
Min / max hair valuen	0.00 / 0.00	0 / 195	0 / 8324
N > 0	0	9	17
Methamphetamine			
Hair analysis pg/mgd	0.00 (0.00)	0.00 (0.00)	42.2 (152.04)
Min / max hair value	0.00 / 0.00	0.00 / 0.00	0 / 730
N > 0	0	0	3
Cocaine			
Hair analysis pg/mg	0.00 (0.00)	63.8 (111.5)	3893 (5554)
Min / max hair value	0.00 / 0.00	0 / 445	73 / 24500
N > 0	0	10	25
MPH			
Hair analysis pg/mgd	0.00 (0.00)	0.00 (0.00)	3.98 (17.93)
Min / max hair value	0.00 / 0.00	0 / 0	0 / 98.5
N > 0	0	0	2
Morphine			
Hair analysis pg/mgd	0.00 (0.00)	0.00 (0.00)	8 (40)
Min / max hair value	0.00 / 0.00	0 / 0	0 / 200
N > 0	0	0	1
Codeine			
Hair analysis pg/mgd	0.00 (0.00), n=32	0.00 (0.00), n=3	106.11 (307.24), n=9
Min / max hair value	0.00 / 0.00	0 / 0	0 / 925
N > 0	0	0	2
Methadone			
Hair analysis pg/mgd	0.00 (0.00)	0.00 (0.00)	2.4 (12)
Min / max hair value	0.00 / 0.00	0 / 0	0 / 60
N > 0	0	0	1
2C-B			
Hair analysis pg/mgd	0.00 (0.00), n=10	4.4 (15.4), n=25	11 (24.56), n=11
Min / max hair value	0.00 / 0.00	0 / 63	0 / 65
N > 0	0	2	2
Ketamine			
Hair analysis pg/mgd	0.00 (0.00), n=10	13.26 (52.86), n=23	89.8 (127.52), n=10
Min / max hair value	0.00 / 0.00	0 / 250	0 / 380
N > 0	0	2	5

Means, standard deviations, minimum and maximum for metabolites (pg/mg) are shown. If hair analyses were not available for some participants, sample size n for participants with hair analyses is shown. The cocaine metabolites benzoylecgonine, cocaethylene, and norcocaine are not shown. Tramadol and 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidene (EDDP) are not shown because they were not detected.

EDDP, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidene; MDA, 3,4-Methylendioxyamphetamine; MDEA, 3,4-Methylendioxy-N-ethylamphetmanine; MDMA, 3,4-Methylendioxy-N-methylamphetmanine; 2C-B, 2,5-dimethoxy-4-bromphenethylamine.

Table 2: Demographic data and drug use (means and standard deviations)

	Controls	**Primary MDMA**	**Polydrug MDMA**	***value***	***p***	**df**
n	56	26	25			
Age, years	25.8 (6.1)	26.6 (7.0)	26.7 (5.8)	0.25	0.78	2
Years of school education	11.02 (1.6)	10.5 (1.8)	10.2 (1.9)	2.14	0.12	2
Verbal intelligence	103.9 (8.2)	102.8 (8.3)	100.9 (8.3)	1.15	0.32	2
Beck's Depression Inventory	3.5 (3.8)	4.4 (4.8)	5.2 (4.9)	1.29	0.28	2
ADHD-SR score	7.7 (5.1)	12.8 (8.5)**	11.76 (7.7)*	6.57	**0.00**	2
ADHD (y/n)[a]	0/56	3/23	4/21	8.64	**.01**	2
Sex (female/male)	26/30	15/11	9/16	2.41	0.30	2
Tobacco						
Smoking status (y/n)[b]	41/15	18/8	24/1*[#]	6.53	**0.04**	2
Cigarettes per day[b]	7.3 (10.1)	5.6 (8.2)	11.8 (7.6)*[#]	3.30	**0.04**	2
Years of use	6.0 (6.6)	4.5 (6.1)	8.8 (5.6)[#]	3.05	0.05	2
Alcohol						
Grams per week[b]	117.9 (132.0)	138.1 (119.6)	184.3 (126.5)*	2.33	0.10	2
Years of use	8.7 (6.5)	6.6 (7.1)	8.1 (5.7)	0.99	0.37	2
Cannabis						
Status (y/n)[b]	30/26	19/7	15/10	2.81	0.25	2
Grams per week[b]	0.44 (1.04)	0.60 (1.3)	0.67 (1.4)	0.35	0.70	2
Years of use	3.3 (3.7)	4.4 (5.1)	4.5 (4.5)	0.90	0.41	2
Cumulative dose (grams)	195.7 (504.6)	543.1 (962.8)	767.4 (1153)*	4.69	**0.01**	2
Positive urine testing (n/y)[c,d]	48/7	21/5	21/4	0.60	0.74	2
Last consumption (days)	23.1 (32.9) n=30	18.0 (36.1) n=19	12.7 (23.3) n=15	0.55	0.58	2
Last consumption (range, days)[e]	3 / 111	3 / 152	3 / 91			
MDMA						
Tablets per week[b,f]	0.00 (0.00)	0.91 (0.89)***	0.8 (1.1)***	23.07	**0.00**	2
Years of use	0.00 (0.00)	3.4 (3.2)***	3.6 (2.5)***	41.64	**0.00**	
Cumulative dose (grams)	0.01 (0.04)	26.6 (32.3)***	21.1 (30.2)***	17.66	**0.00**	2
Last consumption (days)	-	25.9 (21.4) n=26	43.0 (79.1) n=20	1.12	0.30	1
Last consumption (range, days)[e]	-	4 / 98	4 / 365			
Amphetamine						
Status (y/n)[b]	0/56	12/14***	18/7***	50.00	**0.00**	2
Grams per week[b]	0.00 (0.00)	0.01 (0.02)	0.11 (0.14)***[###]	22.93	**0.00**	2
Years of use	0.00 (0.00)	1.9 (3.3)***	2.2 (2.9)***	12.34	**0.00**	2
Last consumption (days)	-	34.1 (44.3) n=12	27.6 (25.2) n=18	0.26	0.61	1
Last consumption (range, days)[e]	-	3 / 122	5 / 91			
Cumulative dose (grams)	0.01 (0.03)	35.0 (129.6)*	26.0 (57.9)	2.79	0.07	2
Positive urine testing (n/y)[c,d]	55/0	26/0	24/1	3.27	0.20	2
Cocaine						
Status (y/n)[b]	0/56	10/16***	22/3***[###]	65.05	**0.00**	2
Grams per week[b]	0.00 (0.00)	0.03 (0.08)	0.62 (0.72)***[###]	29.35	**0.00**	2
Years of use	0.00 (0.00)	1.4 (3.1)*	4.9 (4.3)***[###]	32.36	**0.00**	2
Last consumption (days)	-	33.8 (40.9) n=10,9/57	19.2 (23.5) n=22, 5/22	1.65	0.21	1
Last consumption (range, days)[e]	-	4 / 122	3 / 91			

Cumulative dose (grams)	0.02 (0.05)	41.1 (162.3)	198.4 (259.1)***###	15.60	**0.00**	2
Positive urine testing (n/y)[c,d]	55/0	26/0	22/3*	10.00	**0.01**	2
Ketamin						
Status (y/n)[b]	0/56	2/24	6/19***	14.40	**0.00**	2
Last consumption (days)	-	60.0 (17.0) n=2	244 (257.8) n=6	-	-	-
Last consumption (range, days)[e]	-	14 / 21	5 / 196			
Cumulative occasions	0.00 (0.00)	1.31 (3.98)	2.86 (5.17)	7.26	**0.00**	2

Significant *p*-values ($p<.05$) are shown in bold. Statistical tests: ANOVA (all groups), $\chi 2$ test (all groups) for frequency data or independent t test (two groups).
ADHD, attention-deficit/hyperactivity disorder;
Consumption per week, duration of use, and cumulative dose are averages within the total group.
Last consumption is an average only for persons who reported to have used the drug within the past 6 months. In this case, sample size (n) is shown.
[a]According to DSM-IV criteria.
[b]During the past 6 months.
[c]For cut-offs, see the Supplementary Methods S2.
[d]One urine sample (control) was missing.
[e]min / max
[f]In 100-mg tablets.
Post-hoc tests vs. controls: *p <.05, ** p <.01, ***p <.001; vs. primary MDMA $^{\#}p$ <.05, $^{\#\#}p$ <.01, $^{\#\#\#}p$ <.001.

2.4.2 Cognition

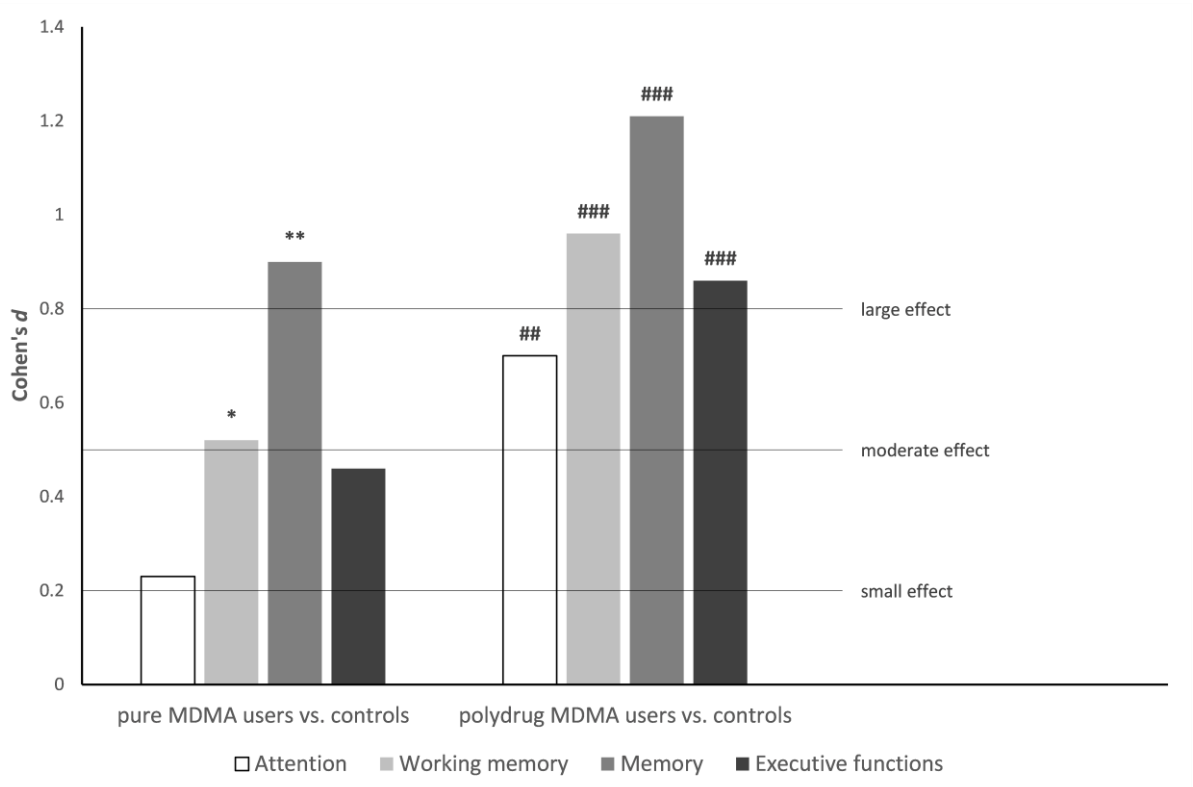
Significant regression equations with the dummy coded group variables were found for all four z-transformed domains of attention ($F(2,104)=4.591$, $p<.05$), working memory ($F(2,104)=9.584$, $p<.001$), declarative memory ($F(2,104)=21.187$, $p<.001$), and executive functions ($F(2,104)=7.297$, $p<.01$). Group differences between controls and polydrug MDMA users were significant for all four domains ($p<.01$-$.001$), whereas group differences between controls and primary MDMA users only reached significance for working memory ($p<.05$) and declarative memory ($p<.01$) performance (Table 3). Effect sizes for performance differences over the four domains are shown in Figure 1. For polydrug MDMA vs. controls, working memory, declarative memory and executive functions reached large effect sizes (d=0.96, 1.21, and 0.86 respectively), while attention difficulties reached a moderate to large effect size (d=0.70). For the comparison of primary MDMA users and controls, only declarative memory impairments reached a large effect size (d=0.90), whereas working memory as well as executive functions displayed moderate and attention only small effect sizes. Accordingly, for the single cognitive parameters depicted in Figure 2, only comparisons between polydrug MDMA users and controls reached large effect sizes of 0.8 and higher. For primary MDMA users vs. controls, the largest effect sizes were found for verbal (RAVLT) and visuo-spatial (PAL) declarative memory measures.

Table 3: Cognitive parameters and domain scores.

				Controls vs. primary MDMA	Controls vs. polydrug MDMA	Primary vs. polydrug MDMA
Cognitive parameters and domain scores	**Controls**	**Primary MDMA users**	**Polydrug MDMA users**	***p***	***p***	***p***
n	56	26	25			
Attention	0.00 (0.78)	-0.19 (0.86)	-0.61 (0.95)	.350	**.003**	.074
RAVLT Supraspan trial 1	9.6 (2.6)	8.8 (2.0)	7.9 (2.4)	.182	**.003**	.152
RVP Discrimination performance A'	0.92 (0.04)	0.92 (0.05)	0.90 (0.05)	.575	**.023**	.135
RVP Total hits	18.8 (4.3)	18.3 (5.0)	16.4 (5.1)	.652	**.040**	.162
Working memory	0.00 (0.60)	-0.36 (0.79)	-0.7 (0.9)	**.034**	**.000**	.064
LNST Score	15.9 (3.1)	15.2 (2.8)	13.8 (2.1)	.356	**.008**	.126
SWM Total errors[a]	15.6 (12.2)	17.9 (15.7)	22.8 (16.4)	.498	**.040**	.222
PAL First trial memory score	16.9 (2.6)	15.1 (3.4)	14.2 (3.1)	**.011**	**.000**	.248
Memory	0.00 (0.76)	-0.77 (0.81)	-1.7 (1.8)	**.004**	**.000**	**.003**
RAVLT Learning performance	64.8 (6.0)	60.8 (5.4)	56.4 (8.3)	**.011**	**.000**	**.040**
RAVLT Delayed recall	14.0 (1.5)	12.7 (1.6)	11.4 (2.5)	**.004**	**.000**	**.029**
RAVLT Recognition performance adj.	0.91 (0.08)	0.86 (0.07)	0.8 (0.2)	**.038**	**.001**	.202
PAL Total trials adj.	7.2 (1.5)	8.3 (2.2)	10.1 (3.7)	**.046**	**.000**	**.014**
PAL Total errors adj.	5.6 (4.3)	9.5 (7.0)	17.8 (19.0)	.106	**.000**	**.008**
Executive functions	0.00 (0.66)	-0.36 (0.96)	-0.81 (1.2)	.093	**.000**	.073
RAVLT Recall consistency (%)	94.7 (4.6)	90.6 (5.4)	86.6 (8.9)	**.005**	**.000**	**.033**
SWM Strategy score[a]	31.7 (5.4)	30.5 (6.1)	33.7 (4.1)	.378	.127	**.041**
IED Total trials adj.	97.2 (49.9)	36.7 (44.6)	44.1 (54.9)	.243	.060	.525
IED Total errors adj.	26.3 (28.7)	116.4 (76.4)	131.0 (95.3)	.273	.086	.581

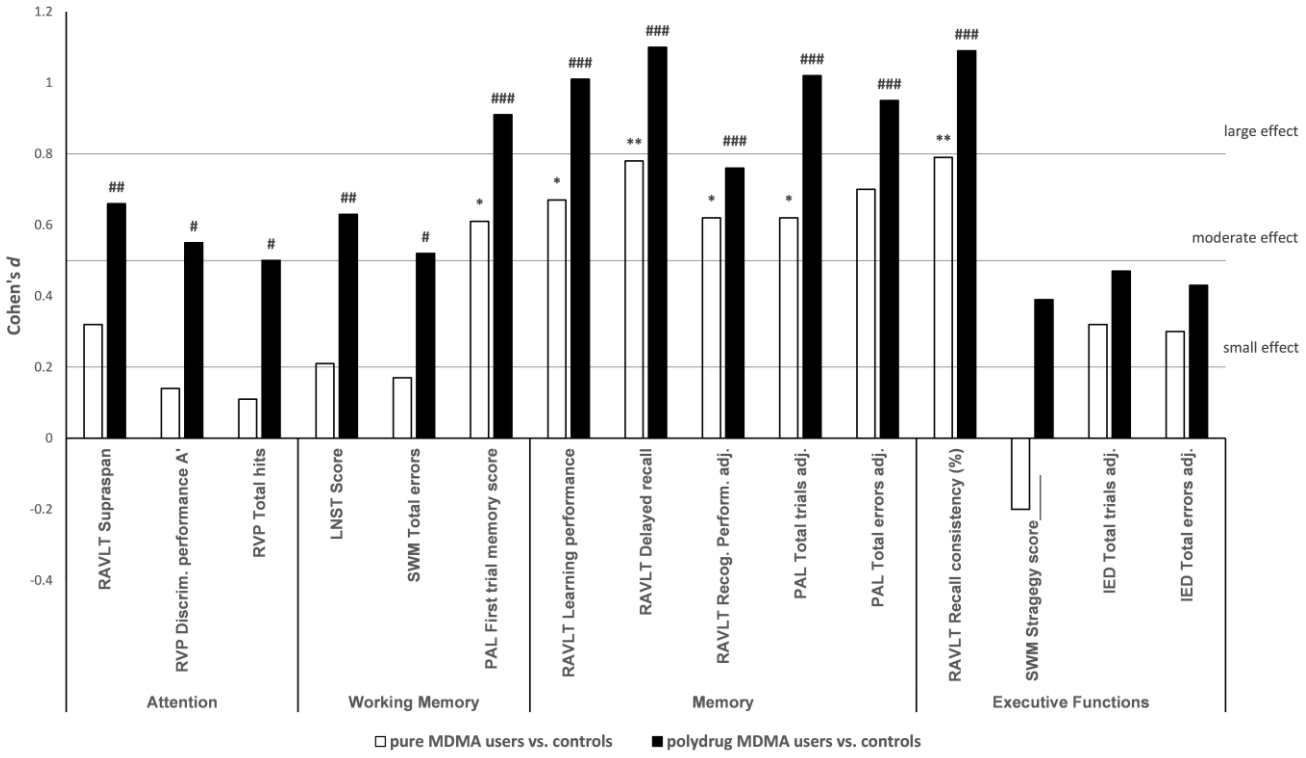
Significant *p*-values ($p<.05$) are shown in bold. Statistical tests: Multiple linear regression with the dummy coded factors controls vs. primary MDMA users and controls vs. polydrug MDMA users (t-test) or polydrug MDMA users vs. controls and polydrug MDMA users vs. primary MDMA users.
IED, Intra-Extra Dimensional Set Shift Task; LNST, Letter Number Sequencing Task; PAL, Paired Associates Learning; RAVLT, Rey Auditory Verbal Learning Test; RVP, Rapid Visual Information Processing; SWM, Spatial Working Memory.
[a] Data of one participant (polydrug MDMA) are missing due to a technical failure.

Figure 1: Cohen's *d* effect sizes for primary and polydrug MDMA users vs. controls over the cognitive domains.



Significant dummy coded group contrasts of controls (n=56) vs. primary MDMA users (n=26): *p<.05, **p<.01; vs. polydrug MDMA users (n=25): $^{\#\#}p$<.01, $^{\#\#\#}p$<.001 are shown.

Figure 2: Cohen's *d* effect sizes for primary and polydrug MDMA users vs. controls over single parameters.



Significant dummy coded group contrasts of controls (n=56) vs. primary MDMA users (n=26): **p*<.05, ***p*<.01; vs. polydrug MDMA users (n=25): $^{\#}p$<.05, $^{\#\#}p$<.01, $^{\#\#\#}p$<.001 are shown.
IED, Intra-Extra Dimensional Set Shift Task; LNST, Letter Number Sequencing Task; PAL, Paired Associates Learning; RAVLT, Rey Auditory Verbal Learning Test; RVP, Rapid Visual Information Processing; SWM, Spatial Working Memory.

2.4.3 Regression models

To analyze potential cofactors and dose-response effects on declarative memory performance multiple regression analyses were performed. These analyses over all participants (n=106) for demographic variables (age, sex, and verbal IQ) and group contrasts revealed that being either a primary or a polydrug MDMA user significantly decreases the intercept of the regression equation of declarative memory performance (β=-.232, t=-2.76, p<.01, and β=-.508, t=-5.97, *p*<.001). As expected, the significant coefficients for age and verbal IQ were negative and positive respectively. The regression model was significant (R^2=0.37, $F_{5, 105}$=11.753, *p*<.001). The model only explained 2.1% more variance after adding the BDI and the ADHD-SR sum score in a second step (*p*=.183) (Supplementary Table S2). Neither of the two variables predicted declarative memory performance significantly (*p*=.101 and *p*=.130).

The association between declarative memory performance and drug use parameters was assessed with two models covering either the past six month (Model 1) or lifetime substance use (Model 2) of the MDMA users (n=51). Model 1 contained the following variables: cannabis consumption in grams per week, the amount of cigarettes smoked per day, amount of alcohol consumed per week, MDMA hair concentration, and a grouping variable that differentiated between primary and polydrug MDMA users to account for stimulant use (Supplementary Table S3). None of the drug parameters predicted declarative memory performance. However, the grouping variable showed that polydrug substance use decreased the intercept (t=-1.93, *p*=.059, β=-.279).

Model 2, which contained drug use parameters concerning lifetime drug consumption, revealed that – within MDMA users – lifetime cannabis consumption predicted declarative memory performance (*p*<.05) when duration of alcohol and nicotine use and lifetime MDMA consumption were held constant (Supplementary Table S4).

2.5 Discussion

The aim of the study was to investigate the cognitive performance of objectively verified, primary and largely pure MDMA users. Detailed psychiatric diagnostics, hair toxicology, and an exact matching procedure minimized the influence of psychiatric comorbidities and underreported drug use. We demonstrated that primary and polydrug long-term MDMA users show medium to strong cognitive impairments in declarative memory and that, in contrast to polydrug MDMA users, primary MDMA users show only small and moderate impairments in the domains of attention, working memory, and executive functions compared with drug-naïve controls. The data of this study confirm previously shown memory deficits in abstinent long-term MDMA users and thus deliver evidence for declarative memory impairments even in largely pure recreational MDMA users with no or minimal stimulant co-use.

In line with previous meta-analyses (Kalechstein et al., 2007; Laws and Kokkalis, 2007; Rogers et al., 2009), our data show that the strongest impairments have to be expected in declarative memory functions after repeated MDMA consumption, which confirms our hypothesis. Task-specifically, decreased delayed verbal memory performance (RAVLT) can be considered the "main symptom" of MDMA misuse as the variable *delayed recall* has been repeatedly shown to differentiate between MDMA users and controls (Reneman et al., 2000; Fox et al., 2001; Quednow et al., 2006) and revealed the strongest effect size in this study for polydrug MDMA users as well as for primary MDMA users. In line with previous findings (Laws and Kokkalis, 2007), effect sizes for verbal memory deficits were larger than for visual memory deficits in MDMA users. Regarding the PAL measures, our data are in accordance with previous studies showing that polydrug MDMA users required more trials to complete the task compared to polydrug controls (Fox et al., 2002). Taken together, the individual variables of our declarative memory domain indicate moderate to large impairments (d=0.62-1.1) in visual, spatial and verbal learning and recognition processes.

Regarding working memory deficits, the primary MDMA users performed worse than controls on the domain level only with a medium effect size (d=0.52), whereas polydrug MDMA users showed strong working memory impairments (d=0.96). This discrepancy in performance may explain the inconsistencies in previous findings and underline the additional detrimental effect of stimulant use on working memory (Vonmoos et al., 2013; 2014). Interestingly, primary MDMA users did not differ substantially from controls in two out of three measures for working memory, *LNST score* and *total errors in the SWM task*. Both measures are widely accepted measures for working memory performance (Morris et al., 1988; Crowe, 2000) and have previously been linked to MDMA-induced deficits (Fox et al., 2002; 2005). Our data do not replicate these findings for largely pure MDMA users but support our hypothesis that working memory deficits in polydrug MDMA users are likely stimulant-driven, and consequently, that past findings may be explained by undetected stimulant co-

consumption. It is noteworthy that – although our working memory domain differentiated significantly between controls and primary MDMA users – only the underlying *first trial memory score* (PAL) reached significance. This variable was viewed as a measure for passive storage ability and has shown to correlate stronger with verbal than with non-verbal memory parameters, probably because subjects verbalize the patterns and/or places which have to be remembered (Torgersen et al., 2012). In the context of Fox et al.'s (2001) suggestion that verbal learning problems in MDMA users are associated with storage and retrieval problems, and the finding that MDMA use affects verbal memory more strongly than visual memory, it can be argued that working memory performance between primary MDMA users and controls might in sum be less impaired then our working memory domain suggests at a first glance. Alternatively, the moderate working memory impairment displayed by our primary MDMA user group might be a result of past stimulant consumption, which may have occurred before the time span captured by the hair analyses. This idea is supported by a significant negative correlation between working memory performance and self-reported lifetime cocaine consumption across all MDMA users ($r(49)=-.40$, $p<.01$).

For primary MDMA users, we did not find any significant results in the domains of executive functions and attention except for the RAVLT parameter *recall consistency*, which contrasts with previous studies that found executive function and decision-making impairments in MDMA users (Fisk et al., 2004; Montgomery et al., 2005; Quednow et al., 2007; Fisk and Montgomery, 2009; Roberts et al., 2016b). On the other hand, Montgomery et al. (2005) – who investigated the executive functions specifically – found no impairments in MDMA users compared to controls in switching, which is – besides updating – tested by the Intra-Extra Dimensional Set Shift Task (IED) applied in the present study. In line with Montgomery et al. (2005) we did not find changes in the IED performance in primary MDMA users. Interestingly, the only variable assessing executive functions that reached significance (*recall consistency*, RAVLT) strongly involves verbal memory in contrast to the other, non-significant variables involving visual memory processes. As mentioned before, results vary regarding attentional performance of MDMA users, which is also reflected in our results; in all three parameters measuring attention, the polydrug MDMA users performed significantly worse than controls with moderate effect sizes, whereas primary MDMA users did not differ substantially from controls. These results are in line with previous research as 1) stimulant users were shown to perform worse than drug-naïve controls in an equally created attention domain (Vonmoos et al., 2013), and 2) as basic attentional and executive functions are generally unaffected in MDMA users compared to polydrug or cannabis using control groups (Parrott, 2001; Medina et al., 2005; Rogers et al., 2009). Interestingly, in contrast to our polydrug MDMA users, largely pure cocaine users did not differ from stimulant-naïve controls in the RAVLT *supraspan* in a previous study from our lab (Vonmoos et al., 2013). Future research should therefore investigate possible interaction effects of MDMA and stimulant consumption more in depth, especially because animal studies revealed that the simultaneous administration of MDMA (or MDMA analogues) and a prodopaminergic agent leads to

a potentiation of the serotonin neurotoxicity of MDMA (Johnson et al., 1991; Johnson and Nichols, 1991; Schmidt et al., 1991; Clemens et al., 2005).

The results of our regression analysis for demographic variables support the notion of declarative memory deficits in abstinent primary MDMA users, as group contrasts remained significant even when sex, age, and verbal IQ were held constant. By adding the BDI and ADHD-SR sum core, the model only improved marginally. We have previously investigated the effects of depression and ADHD symptoms on cognitive performance in cocaine users and found that both factors, ADHD and depression scores, were associated with worse cognitive performance in cocaine users (Vonmoos et al., 2013; Wunderli et al., 2016). We therefore expected to find significant contributions of these two variables in the regression model again. However, probably due to the relative small variance in BDI and ADHS-SR scores and the matching process (exclusion of psychiatric disorders), declarative memory was not significantly predicted through these two measures.

Model 1, which predicted declarative memory performance through drug use parameters covering the past six months, revealed no significant associations except for the grouping variable that distinguished between primary and polydrug MDMA users. Although this grouping variable only predicted declarative memory performance by trend ($p=.059$), the importance of stimulant co-consumption is emphasized by the fact that polydrug MDMA users displayed higher – although none significantly higher – mean values in all of the other predictors.

In Model 2, declarative memory performance was aimed to be predicted by factors covering cumulative lifetime drug use estimates. Although the whole model predicted declarative memory performance by trend only, it revealed that the estimated lifetime dose of cannabis was negatively associated with memory performance. Additionally, the grouping variable still predicted memory performance with constant drug factors by trend. It was postulated previously that cognitive deficits in MDMA users can be explained by cannabis co-use alone (Croft et al., 2001). Our data do not support this assumption because the two user groups still differ in declarative memory performance when the effect of cannabis consumption is held constant. This finding is therefore in line with previous studies demonstrating memory deficits in MDMA users, even when concomitant cannabis use was introduced as a covariate or when MDMA users were compared to cannabis using controls (Fox et al., 2001; Quednow et al., 2006). However, our results support the notion that cannabis is an important confound when cognitive performance is measured in MDMA users (Croft et al., 2001; Simon and Mattick, 2002), although the cannabis use intensity was relatively low in our sample.

Finally, in both models, severity of MDMA consumption did not predict declarative memory performance (MDMA hair concentration and lifetime dose). Previous literature is inconclusive about the correlation between MDMA dose and strength of impairments. Many researchers reported dose-related impairments in MDMA users (Bolla et al., 1998; Gouzoulis-Mayfrank et al., 2000; Montgomery et al., 2005; Quednow et al., 2006). These findings were usually interpreted as evidence

for selective, neurotoxic effects on the 5-HT system (Parrott, 2002; Gouzoulis-Mayfrank et al., 2003; Quednow et al., 2004; Quednow et al., 2006). On the other hand, Laws and Kokkalis (2007) found no continuous relationship of lifetime MDMA consumption of MDMA and memory measures in their meta-analysis and therefore proposed a rather stepwise relationship between MDMA use and memory decline. This explanation is in line with a recent, longitudinal study that only found marginally significant changes in recall measures in stimulant-using polydrug MDMA users over a 2 year period (Wagner et al., 2015). Because neither MDMA hair concentrations nor self-reported amount of lifetime MDMA consumption significantly predicted memory performance, our data support this model of a stepwise relationship between MDMA use and memory decline. Moreover, also duration of abstinence did not predict memory performance in our sample (β=.010, t=0.70, p=.945). An alternative explanation of these discrepancies may lie in the variability of the purity of MDMA tablets potentially leading to different results across studies (Morgan, 1999; Parrott, 2004). In fact, recent analyses in the context of the Swiss Drug Checking program showed that only 7.1% of the ecstasy samples (n=210) tested in 2016 contained psychoactive substances other than MDMA (see http://www.saferparty.ch/125.html).

This study has some limitations. First, human MDMA research practice was criticized for applying unreliable self-reported drug assessments (Cole, 2014). Although we objectively quantified participants drug use via hair analyses, we had to rely on participants self-reports for alcohol, nicotine, and cannabis consumption. Obviously, in a sample in which memory deficits can be expected, self-reported drug assessment might be less reliable. Nonetheless, we aimed to minimize the influence of these drugs by matching the groups accordingly. Second, there is the possibility that cognitive differences are based on pre-existing differences and that predispositions are responsible for drug use and cognitive impairments. This limitation can be controlled by adding a polydrug control group. However, the present investigation is a cross-sectional study that is not suitable to differentiate between predisposing factors and drug-induced alterations.

Taken together, our data suggest that the combined use of MDMA and stimulants is associated with a strongly increased risk for cognitive impairments compared to primary MDMA consumption and that the pronounced working memory and executive function impairments in polydrug MDMA users are likely driven by stimulant co-use. However, primary MDMA users showed robust and strong alterations of declarative long-term memory. The considerable performance difference of primary vs. polydrug MDMA users together with the finding that cannabis additionally impairs memory performance in MDMA users highlights the need for objective group assessments in human MDMA research. Future research should therefore distinguish between stimulant using and primary MDMA users while the influence of other drugs of abuse but especially cannabis consumption should be either excluded or controlled for by matching or an additional cannabis-only user group.

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Conflict of Interest

All authors declare no competing interests and no potential conflict of interest with respect to the research, authorship, and publication of this article.

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2.7 Supplementary material

2.7.1 Methods

Methods S1: Urine and hair toxicology

Urine toxicology analyses comprised the following substances: tetrahydrocannabinol, cocaine, amphetamines, benzodiazepines, opioids, and methadone and were assessed by a semi-quantitative enzyme multiplied immunoassay method using a Dimension RXL Max (Siemens, Erlangen, Germany). For the detection of illegal drug use, the following cut-offs have been applied (Bush, 2008): Cannabis, 50 ng/ml; cocaine, 150 ng/ml; and amphetamines, 500 ng/ml.

To objectively characterize drug use over the last six months, hair samples were collected and analyzed with liquid chromatography-tandem mass spectrometry (LC-MS/MS). The proximal hair segment of a length of up to 6 cm was examined. The following 17 compounds were assessed: cocaine, benzoylecgonine, cocaethylene, norcocaine, amphetamine, methamphetamine, MDMA, MDEA, MDA, morphine, codeine, methadone, EDDP (primary methadone metabolite, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidene), tramadol, 2C-B, ketamine, and methylphenidate.

For our routine protocol for drugs of abuse analysis a three-step washing procedure with water (2 minutes shaking, 15ml), acetone (2min., 10ml) and finally hexane (2min., 10ml) of hair was performed. Then the hair samples were dried at ambient temperatures, cut into small snippets and extracted in two steps, first with methanol (5ml, 16 hours, ultrasonication) and a second step with 3 ml MeOH acidified with 50 µL hydrochloric acid 33 % (3 hours, ultrasonication). The extracts were dried and the residue reconstituted with 50 µL MeOH and 500 µL 0.2 mM ammonium formate (analytical grade) in water. As internal standards deuterated standards of the following compounds were used, added as mixture of the following compounds: cocaine-d3, benzoylecgonine-d3, ethylcocaine-d3, morphine-d3, MAM-d3, codeine-d3, dihydrocodeine-d3, amphetamine-d6, methamphetamine-d9, MDMA-d5. MDEA-d6, MDA-d5, methadone-d9, EDDP-d3, methylphenidate-d9, tramadol-d3, oxycodone-d3, and ephedrine-d3. All deuterated standards were from ReseaChem (Burgdorf, Switzerland), the solvents for washing and extraction were of analysis grade and obtained from Merck (Darmstadt, Germany); LC-solvents were of HPLC grade and were obtained from Sigma Aldrich (Buchs, Switzerland).

The LC-MS/MS apparatus was an ABSciex QTrap 3200 (Analyst software Version 1.5, Turbo V ion source operated in the ESI mode, gas 1, nitrogen (50 psi); gas 2, nitrogen (60 psi); ion spray voltage, 3500V; ion source temperature, 450°C; curtain gas, nitrogen (20 psi) collision gas, medium), with a Shimadzu Prominence LC-system (Shimadzu CBM 20 A controller, two Shimadzu LC 20 AD pumps including a degasser, a Shimadzu SIL 20 AC autosampler and a Shimadzu CTO 20 AC column oven, Shimadzu, Duisburg, Germany). Gradient elution was performed on a separation column (Synergi 4µ POLAR-RP 80A, 150x2.0 with a POLAR-RP 4x2.0 Security Guard Cartridge, (Phenomenex, Aschaffenburg, Germany). The mobile phase consisted of 1mM ammonium formate buffer adjusted to

pH 3,5 with formic acid (eluent A) and acetonitrile containing 1mM ammonium formate and 1 mM formic acid (eluent B). The analysis was performed in MRM mode with two transitions per analyte and one transition for each deuterated internal standard, respectively. According to the Society of Hair Testing (Society of Hair, 2004), the following cut-offs have been applied: cocaine, 500 pg/mg; amphetamine, 200 pg/mg; and MDMA, 200 pg/mg.

Methods S2: Construction of cognitive domain scores

Fifteen predefined main cognitive test parameters were z-transformed on the basis of means and standard deviations of the control group as published before (Vonmoos et al., 2013). If necessary, test scores were reversed so that high scores always indicated a better cognitive performance. These parameters were reduced to the four cognitive domains attention, working memory, declarative memory, and executive function. Furthermore, these four z-scored domains were equally integrated into a broad global cognitive index (GCI).

Attention: To assess attentional capacity, we focused primarily on sustained attention by including the two Rapid Visual Information Processing (RVP) parameters discrimination performance A' and total of hits (Jones et al., 1992). In order to diversify this domain we added the Ray Auditory Verbal Learning Test (RAVLT) parameter trial 1, a supraspan measure with a large attentional component (Lezak et al., 2004).

Working Memory: The Spatial Working Memory (SWM) parameter number of total errors tested the capability to retain spatial information and to manipulate remembered items in working memory (Morris et al., 1988). The Letter Number Sequencing Test (LNST) measured the verbal working memory by summing up the number of correct responses (Wechsler, 1997). The third parameter was the number of correctly located patterns after the first presentation, a Paired Associates Learning (PAL) parameter measuring primarily a visual working memory component (Sahakian et al., 1988).

Declarative memory: The RAVLT was administered to assess the verbal declarative memory performance (Helmstaedter et al., 2001). Performance was measured by the parameters *learning performance* (∑trials 1-5), delayed recall (trial 7), and an adjusted recognition performance (*p(A)) (Helmstaedter et al., 2001).* To capture the visual declarative memory, we used the two PAL parameters: adjusted total of errors and adjusted total of trials (Sahakian et al., 1988).

Executive Functions: The Intra/Extra-Dimensional Set Shifting Task (IED) assessed visual discrimination, attentional set formation, maintenance, shifting, and flexibility (Downes et al., 1989). The considered test parameters were the total of errors and trials adjusted to the amount of completed stages. Hereby, we added the SWM strategy score assessing the applied heuristic strategies (Morris et al., 1988), and the RAVLT recall consistency, a parameter impaired in patients with prefrontal lesions (Jokeit et al., 1997; Alexander et al., 2003; Benedict et al., 2005) and related with measures of executive functions (Beebe et al., 2000).

2.7.2 Results

Table S1. Hair analyses results (concentratin calues in pg/mg) and MDMA group allocation.

Subject	Hair sample taken?	MDMA group	MDMA	MDEA	MDA	Amphet-amine	Methamphet-amine	Cocaine	Methyl-phenidate	Morphine/ Codeine	Methadone/ EDDP	2C-B	Ketamine	Hair length[1]
1	yes	primary	1985	0	55	0	0	445	0	0	0	0	n.a.	6
2	yes	primary	975	0	30	55	0	45	0	0	0	n.a.	n.a.	6
3	yes	primary	48000	40	150	60	0	80	0	0	0	0	n.a.	3.5
4	yes	primary	1673	0	102	0	0	0	0	0	0	47	0	6
5	yes	primary	915	0	45	59	0	156	0	0	0	0	0	2
6	yes	primary	780	21	50	0	0	169	0	0	0	0	0	6
7	yes	primary	4813	0	244	25	0	0	0	0	0	0	0	6
8	yes	primary	2239	0	121	0	0	0	0	0	0	0	0	3.5
9	yes	primary	2982	0	165	0	0	298	0	0	0	63	0	6
10	yes	primary	1440	0	60	122	0	0	0	0	0	0	0	3.5
11	yes	primary	626	0	41	0	0	0	0	0	0	0	0	6
12	yes	primary	2408	114	117	160	0	0	0	0	0	0	0	6
13	yes	primary	1763	0	125	15	0	0	0	0	0	0	0	6
14	yes	primary	1054	0	60	191	0	78	0	0	0	0	250	6
15	yes	primary	231	0	6	0	0	0	0	0	0	0	0	6
16	yes	primary	1369	0	67	0	0	0	0	0	0	0	0	4
17	yes	primary	2510	20	79	0	0	0	0	0	0	0	0	6
18	yes	primary	534	0	9	0	0	0	0	0	0	0	0	6
19	yes	primary	4670	0	331	0	0	81	0	0	0	0	0	6
20	yes	primary	2695	0	182	0	0	0	0	0	0	0	0	6
21	yes	primary	471	0	29	0	0	87	0	0	0	0	0	6
22	yes	primary	2232	0	55	0	0	0	0	0	0	0	55	6
23	yes	primary	32	0	5	0	0	0	0	0	0	0	0	6
24	yes	primary	2625	0	119	195	0	0	0	0	0	0	0	6
25	yes	primary	118	0	0	0	0	0	0	0	0	0	0	6
26	yes	primary	123	0	9	0	0	219	0	0	0	0	0	6
27	yes	poly	17500	0	750	180	0	**7700**	0	0	0	n.a.	n.a.	6
28	yes	poly	10659	43	266	**755**	0	73	0	0	0	0	191	1.5
29	yes	poly	14863	31	317	0	0	**2515**	0	0	0	0	174	5
30	yes	poly	2298	54	117	93	0	**713**	0	0	0	0	0	6
31	yes	poly	754	0	50	0	0	**7233**	0	0	0	0	0	1.5
32	yes	poly	12639	22	144	0	0	**803**	0	0	0	0	0	6
33	yes	poly	6050	0	303	**8324**	245	**4243**	0	0	0	0	31	6
34	yes	poly	15731	29	1088	**4228**	0	**1178**	0	0	0	65	0	6
35	yes	poly	1778	0	116	**540**	0	**1583**	0	0	0	0	122	6
36	yes	poly	134	0	0	**808**	0	88	0	0	0	56	0	6
37	yes	poly	146	0	0	**1013**	0	216	0	0	0	0	380	6
38	yes	poly	4650	0	195	**730**	0	**24500**	0	30	0	n.a.	n.a.	6
39	yes	poly	2000	0	30	140	0	**1000**	0	0	0	n.a.	n.a.	1.5
40	yes	poly	1200	0	20	0	0	**2000**	0	0	0	n.a.	n.a.	3
41	yes	poly	1150	0	100	**325**	0	**1275**	0	0	0	n.a.	n.a.	6
42	yes	poly	850	0	50	0	0	**2800**	0	0	0	n.a.	n.a.	6
43	yes	poly	3150	0	215	105	730	**590**	0	0	0	n.a.	n.a.	6
44	yes	poly	835	0	15	0	0	**2900**	0	925	0	n.a.	n.a.	6
45	yes	poly	6350	0	307.5	0	80	**1750**	0	0	0	n.a.	n.a.	6
46	yes	poly	1000	0	35	0	0	**3300**	0	200	60	n.a.	n.a.	1.5
47	yes	poly	3750	145	150	**1850**	0	**15000**	0	0	0	n.a.	n.a.	6
48	yes	poly	10000	0	250	**440**	0	**10000**	0	0	0	n.a.	n.a.	1.5
49	yes	poly	2050	0	65	**230**	0	**3450**	0	0	0	n.a.	n.a.	6
50	yes	poly	570	0	48	**210**	0	480	10	0	0	n.a.	n.a.	2.5
51	yes	poly	2265	0	67.5	55	0	**1950**	89.5	0	0	n.a.	n.a.	4
52	no	none	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	0	n.a.	n.a.	-
53	no	none	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	0	n.a.	n.a.	-

For each participant, the amount of metabolites per substance (pg/mg) and the group are shown. The cocaine metabolites benzoylecgonine, cocaethylene, and norcocaine are not shown. Tramadol is not shown because it was not detected. Reasons for polydrug MDMA classification are shown in bold.
To be included into the primary MDMA group, hair samples had to reveal a cocaine value <500pg/mg and an amphetamine value <200pg/mg (Cooper et al., 2012).
[1] analyzed hair length from scalp in cm.

EDDP, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidene; MDA, 3,4-Methylendioxyamphetamine; MDEA, 3,4-Methylendioxy-N-ethylamphetmanine; MDMA, 3,4-Methylendioxy-N-methylamphetmanine; n.a., not available; 2C-B, 2,5-dimethoxy-4-bromphenethylamine.

Table S2. Multiple Regression analysis for demographic variables, group contrasts and psychopathology predicting memory performance

	B	SE *B*	β
Step 2			
Constant	-.191	.229	
primary MDMA vs. Controls	-.828	.271	-.270**
poly MDMA vs. Controls	-1.603	.268	-.523***
Sex	-.041	.214	-.016
Age	-.041	.018	-.194*
Verbal IQ	.037	.013	.232**
BDI sum score	-.045	.027	-.150
ADHD sum score	.028	.018	.148

Dependent variable: declarative memory performance (z-score).
N = 106 (26 primary MDMA users, 25 poly MDMA users, and 56 controls).
R^2 = .37 and F = 11.753 (p<.001) for Step 1, ΔR^2 = .021 and ΔF = 1.726 (p = .183) for Step 2.
The data met the assumption of independent errors (Durbin-Watson value = 2.13).
ADHD = Attention Deficit / Hyperactivity Disorder, ADHD sum score = Sum of Items 1 to 18, *B* = regression coefficient, β = standardized Beta, BDI = Beck's Depression Inventory, SE *B* = standard error.
Age is centered at the overall mean age (26.21 years) and verbal IQ is centered at 100 IQ points. Females were coded with 1 and males with 0 for the sex variable.
* *p* <.05, ** *p* <.01, *** *p* <.001

Table S3. Multiple regression analysis for drug use variables covering consumption over the past half year predicting memory performance

	B	*SE B*	*β*
Constant	11.415	6.388	
primary MDMA vs. poly MDMA	-.810	.419	-.279(*)
Cannabis (g/week)	-.232	.152	-.208
Nicotine (cigarettes per day)	-.039	.026	-.224
Alcohol (g/week)	.001	.002	.108
MDMA hair concentration (pg/mg)	.000	.000	.213

Dependent variable: declarative memory performance (z-score).
N = 51 (26 primary MDMA users, 25 poly MDMA users).
R^2 = .21 and F = 2.372 (p=.054).
The data met the assumption of independent errors (Durbin-Watson value = 2.55).
B = regression coefficient, β = standardized Beta, g/week = grams per week, pg/mg = picogram per milligram, SE *B* = standard error.
Poly MDMA users were coded with 1 and primary MDMA users with 0 for the group comparison.
(*) *p* =.059

Table S4. Multiple regression analysis for drug use variables covering consumption over the lifetime predicting memory performance

	B	*SE B*	*β*
Constant	11.232	6.498	
primary MDMA vs. poly MDMA	-.773	.423	-.266(*)
Alcohol (years of use)	-.018	.035	-.080
Nicotine (years of use)	-.016	.039	-.067
Cannabis lifetime dose (g)	-.000	.000	-.271*
MDMA lifetime dose (tablets[1])	-.000	.001	-.011

Dependent variable: declarative memory performance (z-score).
N = 51 (26 primary MDMA users, 25 poly MDMA users).
R^2 = .19 and F = 2.103 (p=.083).
The data met the assumption of independent errors (Durbin-Watson value = 2.40).
B = regression coefficient, β = standardized Beta, g = grams, SE *B* = standard error.
[1] tablets à 100mg
Poly MDMA users were coded with 1 and primary MDMA users with 0 for the group comparison.
(*) *p* =.075, **p*=.052

2.7.3 References

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3 Social cognition and interaction in chronic users of 3,4-methylenedioxymethamphetamine (MDMA, “Ecstasy”)

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Personal Contribution

BBQ designed this study and all authors contributed to its planning, analysis strategy and interpretation of the data. BBQ, MV, LT, CZ, and MDW were responsible for the neuropsychological assessment of the study participants. Qualitative urine and hair testing was performed by MRB and TK. Statistical analyses were conducted by MDW under the supervision of BBQ. All authors had access to the data and the statistical outputs and critically revised the article after MDW had drafted it. All authors approved the final manuscript.

3.1 Abstract

Background. The empathogen 3,4-methylenedioxymethamphetamine (MDMA) is the prototypical prosocial club drug inducing emotional openness to others. It has recently been shown that acutely applied MDMA in fact enhances emotional empathy and prosocial behavior, while it simultaneously decreases cognitive empathy. However, the long-term effects of MDMA use on socio-cognitive functions and social interactions have not been investigated yet. Therefore, we examined emotional and cognitive empathy, social decision-making, and oxytocin plasma levels in chronic MDMA users.

Methods. We tested 38 regular but recently abstinent MDMA users and 56 MDMA-naïve controls with the Movie for the Assessment of Social Cognition (MASC), the Multifaceted Empathy Test (MET), the Distribution Game and the Dictator Game. Drug use was objectively quantified by 6-month hair analyses. Furthermore, oxytocin plasma levels were determined in smaller subgroups (24 MDMA users, 9 controls).

Results. MDMA users showed superior cognitive empathy compared with controls in the MET (Cohen's *d*=.39) and in the MASC (*d*=.50), but they did not differ from controls in emotional empathy. Moreover, MDMA users acted less self-serving in the Distribution Game. However, within MDMA users, multiple regression analyses showed that higher MDMA concentrations in hair were associated with lower cognitive empathy (β_{MDMA}=-.34, t=-2.12, p<.05). Oxytocin plasma concentrations did not significantly differ between both groups.

Conclusions. We conclude that people with high cognitive empathy abilities and pronounced social motivations might be more prone to MDMA consumption. In contrast, long-term MDMA use might nevertheless have a detrimental effect on cognitive empathy capacity.

3.2 Introduction

With an estimated 19.4 million past-year users, 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") remains one of the most used illicit drugs worldwide (United Nations Office on Drugs and Crime, 2016). MDMA is a synthetic substituted amphetamine derivate that blocks and reverses monoamine transporters leading to a rapid release of serotonin (5-HT) and noradrenalin and to a lesser extend dopamine (Rudnick and Wall, 1992; Kalant, 2001). As its main positive subjective effects are enhanced empathy, increased prosocial feelings, and a general sense of well-being, MDMA is regarded as the prototypical prosocial club drug (Vollenweider et al., 1998; Kamilar-Britt and Bedi, 2015). Consequently, in an international survey on drug users, MDMA was ranked highest in the condition of sociability (Morgan et al., 2013).

In animals, the acute effects of MDMA on social behavior have been researched extensively, whereby "adjacent lying" and "friendly following" were consistently reported to be increased in rats (Ando et al., 2006; Thompson et al., 2009). Together with decreased aggression and elevated social reward, literature consistently suggests a prosocial effect profile of MDMA in rodents (Kamilar-Britt and Bedi, 2015). Recently, social cognition has been broadly investigated in MDMA-challenge studies conducted on healthy human volunteers mostly focusing on measures of empathy. The concept of empathy has frequently been conceptualized as entailing *cognitive* and *emotional* components. Cognitive empathy, which comprises inferring or discriminating emotions of others together with *Theory-of-Mind* (ToM), which additionally implicates the ability to deduce the perspective of others, describes the ability to decode and understand another person's mental state (Baron-Cohen and Wheelwright, 2004; Blair, 2005) on a mere cognitive level without considering the persons emotional response. On the other side, emotional empathy is defined as the compassion or the empathizing with the emotions of others (Blair, 2005).

Regarding *cognitive empathy*, acute MDMA intake has repeatedly been shown to reduce the identification of negative emotional stimuli (Bedi et al., 2010; Hysek et al., 2012; Hysek et al., 2014b; Hysek et al., 2014a; Kirkpatrick et al., 2014) and one study additionally found an increased recognition of positive emotional stimuli (Hysek et al., 2012). These valence-dependent acute MDMA effects were – to our knowledge – exclusively found in the *Face Emotion Recognition Task* (FERT) (Bedi et al., 2010; Hysek et al., 2014b) and the *Reading the Mind in the Eyes Test* (RMET) (Hysek et al., 2012). In two other well-established social cognition tasks, namely the *Movie for the Assessment of Social Cognition* (MASC) and the *Multifaceted Empathy Test* (MET), cognitive empathy performance was not affected by acute MDMA intake (Kuypers et al., 2017). By contrast, *emotional empathy* ratings – driven by enhanced responses to emotionally positively charged stimuli – was shown to be increased in the MET under the acute influence of MDMA (Hysek et al., 2014b; Schmid et al., 2014). In summary, research on empathy performance suggests that acute MDMA intake decreases cognitive empathy but enhances emotional empathy (Kamilar-Britt and Bedi, 2015), even though these findings

are limited to specific tasks. Interestingly, these acute prosocial effects of MDMA have been linked to central oxytocin (OXT) release, as several studies have found dose-dependent increases in blood plasma OXT levels right after MDMA administration (Wolff et al., 2006; Dumont et al., 2009; Hysek et al., 2012; Schmid et al., 2014). This increase in plasma OXT levels was shown to correlate with increased prosocial feelings in humans (Dumont et al., 2009).

Interestingly, no study has investigated social cognition in abstinent, long-term MDMA users to date. Thus, we measured cognitive and emotional empathy of relatively pure MDMA users and drug-naïve healthy controls with the MASC and the MET. To measure social decision-making, we additionally applied the Distribution Game and the Dictator Game (Charness and Rabin, 2002; Engelmann and Strobel, 2004). Given that acutely applied MDMA increases plasma levels of OXT (Dumont et al., 2009; Hysek et al., 2012) and that a former animal study documented lasting depletion of brain OXT after long-term MDMA administration (van Nieuwenhuijzen et al., 2010), we additionally investigated blood plasma OXT levels in a subsample of our participants. Finally, as a special feature of our study, we objectively determined drug use through quantitative hair analyses for several reasons. First, MDMA users often co-use other drugs (Schifano et al., 1998; Curran, 2000) and previous MDMA research has been criticized for measuring drug consumption only via self-reports (Cole, 2014). Second, drug users might be motivated to give a biased self-report or simply over- or underestimate their own consumption because of consistently shown memory alterations (Magura and Kang, 1996; Quednow et al., 2006; Wunderli et al., 2017).

Because MDMA has been shown to impair OXT neurotransmission in rats when given chronically (van Nieuwenhuijzen et al., 2010) and because OXT and emotional empathy seem to be functionally linked (Thompson et al., 2007; Kirkpatrick et al., 2014), we hypothesized that chronic MDMA users show a deficit in emotional empathy and display lowered plasma levels of OXT. Alternatively, such deficits could also be preexistent given that the main motivator for MDMA use is to enhance prosocial feelings like feeling closer to other people (Morgan et al., 2013) and to increase *emotional empathy* (Hysek et al., 2014b). Thus, recreational MDMA users might compensate (or self-medicate) a deficit in emotional empathy and lower OXT levels by their drug intake. Lastly, we expected higher MDMA use to be associated with lower cognitive empathy as it was shown by an inverse correlation between lifetime MDMA use and RMET performance in one of our previous studies (Preller et al., 2014).

3.3 Method

3.3.1 Participants

Within the context of the Zurich Cocaine Cognition Study ($ZuCo^2St$) (Vonmoos et al., 2013b; Quednow, 2016), we recruited 53 long-term MDMA users and 56 MDMA-naïve healthy controls by means of online media and flyer advertisements. Candidates underwent a standardized telephone screening to assess their study eligibility prior to testing. All tested participants were aged between 18 and 60 years and had sufficient German language skills. We only included MDMA users whose self-reported drug use was confirmed by hair analyses and whose MDMA hair concentration values exceeded their cocaine and amphetamine concentrations – the most common concomitant drugs in our sample. Primary stimulant users with only a co-consumption of MDMA were thus excluded, as stimulants have been shown to strongly affect social cognition (Quednow, 2017). Furthermore, because of deficient/missing hair samples, two MDMA users were excluded. Following this procedure, 38 participants were identified as MDMA-preferring users and included in the analyses (see Supplementary Table S1 for detailed hair analyses). The MDMA group was matched with 56 MDMA-naïve healthy controls with regard to age, sex, verbal intelligence, years of education, depression scores, and weekly cannabis consumption (Table 1).

Inclusion criteria for the drug using group were MDMA as the primary drug, MDMA use of at least 100 standard doses (one MDMA standard dose corresponds to 100mg crystalline MDMA or one ecstasy pill) or weekly consumption during the last year (>50 occasions), and a current abstinence period of less than six months. Exclusion criteria for the MDMA groups were any acute or previous Axis-I *DSM-IV* adult psychiatric disorders with the exception of MDMA, alcohol, and nicotine abuse and a history of depression (acute major depression was excluded). The general exclusion criteria encompassed current or previous neurological disorders or head injuries, any clinically significant medical disease, a family history of schizophrenia or bipolar disorder, the use of any medication affecting the central nervous system, and a lifetime history of opioid use. Additionally, all participants who reported daily (or more frequent) cannabis consumption were excluded. Controls were also excluded if they fulfilled the diagnostic criteria for any Axis-I *DSM-IV* psychiatric disorder, including any form of substance use disorder (except nicotine and cannabis), or any other current or previous regular illegal drug use.

All participants were asked to abstain from illegal substances for at least three days and from alcohol for at least 24h prior to testing. Drug urine screenings were employed to control for compliance with the abstinence period (see Table 1). The study was approved by the Cantonal Ethics Committee of Zurich. All participants gave written informed consent and were compensated for their participation. Both, MDMA users and MDMA-naïve healthy controls were already published in Wunderli et al. (2017), however polydrug users with hair concentrations of stimulants (e.g., cocaine and

amphetamine) exceeding the values of MDMA were excluded from the present analysis. Moreover, the present MDMA user sample did not overlap with the samples of previous publications from the ZuCo^{2}St including cocaine users and stimulant-naïve controls (e.g., Preller et al., 2013; Vonmoos et al., 2013b; Hulka et al., 2014; Preller et al., 2014). However, about 75% of the present control group has been reported in these previous publications but all participants from the ZuCo^{2}St and the present study were investigated with the same procedure in the same environment and by the same study team.

3.3.2 Clinical assessment

Trained psychologists conducted the *Structured Clinical Interview for Axis-I DSM-IV* disorders (SCID I). Depressive symptoms were assessed with the *Beck Depression Inventory* (BDI) (Beck et al., 1961) because depression might impact social cognition (Schreiter et al., 2013) and ADHD symptoms with the *ADHD Self-Rating Scale* (ADHD-SR) corresponding to *DSM-IV* criteria (Rosler et al., 2004) given that ADHD and drug use were shown to mutually amplify ToM deficits (Wunderli et al., 2016). Premorbid verbal intelligence (verbal IQ) was estimated with a German vocabulary test (*Mehrfachwahl-Wortschatz-Intelligenztest*) (Lehrl et al., 1995). To assess the personality structure of our sample, we further applied the *Barratt Impulsiveness Scale* (BIS-11) (Patton et al., 1995) and the *Temperament Character Inventory* (TCI) (Cloninger, 1994).

3.3.3 Drug use assessment

Self-reported drug use was assessed with the *Interview for Psychotropic Drug Consumption* (Quednow et al., 2004). In addition, to objectively quantify the severity of participant's drug use during the past months, hair samples were taken from the posterior vertex region of the head in order to determine the concentration of 17 common drugs and their metabolites by liquid chromatography-tandem mass spectroscopy (LC-MS/MS). To exclude acute intoxication at testing sessions, urine drug screenings were employed by semi-quantitative enzyme multiplied immunoassays (for technical details see Supplementary Methods S1).

3.3.4 Assessment of empathy and social decision-making

MET

The MET is a computer-based test that consists of 40 pictures of people in emotionally charged situations (Dziobek et al., 2008). Based on the idea that empathy is a multidimensional construct consisting of cognitive and emotional empathy (Davis, 1983), the MET requires the participant to deduce the mental state of the depicted person by choosing which out of four words best describes the person's mental state (cognitive empathy) on one side, and to indicate his/her empathic concern

(explicit emotional empathy) and arousing rate (implicit emotional empathy) on a rating scale (1-9). To avoid multiple testing, we combined (summed up) the implicit and explicit emotional empathy measures (for both negative and positive stimuli) from the MET to an overall emotional empathy score (EES) (see Table 2).

MASC

The MASC was developed with the aim to operationalize social cognition as close to real life as possible and therefore consists of a 15min video that shows four characters spending an evening together. The video stops 45 times and questions about the characters' feelings, thoughts, and intentions are asked (Dziobek et al., 2006). For each question, four different answers are presented whereof one answer represents the correct answer. The wrong answers represent three different mistakes: 1) Instead of mentalizing, the subject explained the situation by physical causation (no ToM), 2) the subject undermentalized (less ToM), and 3) the subject overmentalized (too much ToM). The correct number of answers is the main outcome measure of the MASC. Additionally, we built the cognitive empathy domain score (CES) by averaging the MET cognitive empathy score and the MASC sum score after they were z-transformed on the means and standard deviations of the control group to a combined measure of cognitive empathy.

Distribution Game and Dictator Game

The Distribution Game and the Dictator Game have been described in detail before (Hulka et al., 2014). Notably, in these two monetary distribution games, the participants actually had the chance to gain real money (0.25 Swiss francs per 1 point). In brief, the Distribution Game involves two players. The participant – every time in the position of player A – is requested to choose one out of 10 possible point distributions. In the first distribution, both players receive the same amount of 25 points, which represents the only completely fair distribution. In the most unfair distribution, player A receives 40 points (Payoff A) and player B only one point (Payoff B).

The Dictator Game, which always followed the Distribution Game, involved the same two players, whereby player A was asked to distribute 50 points among himself (Payoff A) and player B (Payoff B). In accordance with a previously published paper from the ZuCo^{2}St (Hulka et al., 2014), we z-transformed the measures of the Distribution and Dictator Game on the means and standard deviation of the control group and equally integrated them into the composite Payoff A and Payoff B scores.

For both games, we analyzed Payoff A as the main dependent variable.

3.3.5 Assessment of blood plasma OXT levels

The blood was collected in 5 ml BD Vacutainer K2EDTA tubes (Vacutainer Systems, becton Dickinson, Plymouth, UK) and immediately mounted on ice. Right after blood collection, the samples were centrifuged at 4000 rpm for 10 min at 4°C to separate the plasma. After pipetting the plasma, it was stored at -80°C until it was analyzed according to procedures employed in previous studies (Neumann et al., 2013; Bosch et al., 2015).

3.3.6 Statistical analysis

We performed the statistical analyses with SPSS 23.0 for Windows. Quantitative data were either analyzed by means of Students t-tests (only demographic data), Mann-Whitney tests, or two-way analyses of covariance (ANCOVA). Frequency data were analyzed by means of Pearson's chi-square tests. We used an alpha level of .05 for all statistical tests. In the ANCOVAs applied to compare empathy between MDMA users and controls, we introduced group and sex as fixed factors, and verbal IQ as a covariate because it was consistently shown that men are less empathic that women (Fukushima and Hiraki, 2006; Knickmeyer et al., 2006; Singer et al., 2006; Rueckert and Naybar, 2008) and because verbal IQ has been proposed to be linked to empathy measures before (Lawrence et al., 2004). Analyzing social decision-making with ANCOVAs, sex was used as a second covariate to verbal IQ given that age is correlated with prosocial behavior (Hulka et al., 2014). We investigated the association between clinical measures and empathy and the association between plasma OXT values and empathy within MDMA users with correlation analyses (Pearson's product-moment and Spearman's rank correlation respectively) whereby we applied a significance threshold of $p<.01$ in order to avoid alpha error accumulation. To be able to assess the strength of group differences and their practical significance between controls and MDMA users, Cohen's *d* effect sizes were calculated based on the means and pooled standard deviations (SD) of the two groups (Cohen, 1988).

To analyze potential co-factors of cognitive empathy, we regressed the CES on the demographic variables age, sex, years of education, and verbal IQ (forced entry) over all participants and over MDMA users only. To analyze drug effects (within MDMA users) on cognitive empathy, we regressed CES on the MDMA hair analyses while retaining those demographic variables in the model that were significantly associated with CES. Because our MDMA user group showed, although minimal, co-consumption of other drugs, we additionally added amphetamine and cocaine hair analyses together with self-reported measures of cannabis, alcohol and nicotine consumption into the model according to previously published investigations of MDMA users (Wunderli et al., 2017). Because some of the drug use variables displayed a right-skewed distribution, we log-transformed ($\log_{10}$) these data after adding the constant 1 to those variables that included 0 values.

Based on a post-hoc power analysis (after participant's drug use was confirmed by hair analyses) with G*Power 3.1.9.2 (Faul et al., 2007), the main effects of the ANCOVAs in this study have an alpha-

error probability of 5% and a power of 80% (assumed 6% variance explained by special effect, 24% variance explained by the covariates, and 70% error variance). The power analysis for our regression model investigating MDMA's effect on cognitive empathy within MDMA users revealed a power of 80% (one-tailed, assumed 13% variance explained by predictor, 12% by verbal IQ and 75% residual variance) (Shamay-Tsoory et al., 2004; Toussaint and Webb, 2005).

3.4 Results

3.4.1 Demographic characteristics and drug use

As intended by the application of our matching procedure, the groups did not differ significantly in sex distribution, age, verbal IQ, years of education, and depression scores (Table 1). For objective drug-use measures, the median hair drug concentration for the MDMA users (n=38) was 2116 pg/mg and the middle 50% of hairs analyses fell between 881 pg/mg and 3530 pg/mg, whereas none of the controls had MDMA in their hairs.

Moreover, 26 out of the 38 investigated MDMA users showed only minimal amphetamine and cocaine hair concentrations below the commonly accepted cut-off values (Society of Hair, 2004) of 200 pg/mg and 500 pg/mg respectively (Table S1). The remaining 12 MDMA users displayed amphetamine and/or cocaine hair concentrations above the mentioned cut-off values, but in each case also showed considerably higher MDMA hair concentrations. Therefore, we included all 38 (preferred) MDMA users to increase the power of our analyses (for detailed hair analyses of all MDMA users see Table S1). For self-reported cannabis parameters, MDMA users did not differ from controls for weekly cannabis use during the past half-year, duration of use, duration since last consumption, and in the amount of positive urine analyses. However, MDMA users reported a larger lifetime dose of cannabis. Finally, MDMA users did not differ from controls in any tobacco or alcohol use measures.

TABLE 1: Demographic data and drug use (means and standard deviations)

	Controls	**MDMA users**	***value***	***p***	**df**
n	56	38			
Age, years	25.8 (6.1)	25.9 (6.2)	-0.09	.93	92
Years of school education	11.0 (1.6)	10.4 (1.9)	1.7	.10	92
Verbal intelligence	103.9 (8.2)	102.7 (8.3)	0.70	.48	92
BDI score	3.5 (3.8)	4.2 (4.4)	-0.73	.47	92
Sex (f/m)	26/30, 46.5 % f	18/20, 47.5% f	0.01	.93	1
Tobacco					
Smoking status (y/n)[a]	41/15, 73.2% y	30/8, 78.9% y	0.40	.53	1
Cigarettes per day[a]	7.3 (10.1)	7.2 (8.7)	0.01	.99	92
Years of use	6.0 (6.6)	5.3 (5.5)	0.60	.55	92
Alcohol					
Status (y/n)[a]	55/1, 98.2% y	38/0, 100.0% y	0.69	.41	1
Grams per week[a]	117.9 (132.0)	151.1 (121.9)	-1.2	.22	92
Years of use	8.7 (6.5)	6.3 (6.1)	1.8	.07	92
Cannabis					
Status (y/n)[a]	30/26, 53.5% y	29/9, 76.3% y	5.0	**.03**	1
Grams per week[a]	0.44 (1.0)	0.60 (1.1)	-0.67	.51	92
Years of use	3.3 (3.7)	4.7 (5)	-1.6	.11	92
Cumulative dose (grams)	195.7 (504.6)	606.8 (1061)	-2.5	**.01**	92
Positive urine testing (n/y)[b]	48/7, 12,5% y	31/7, 18,4% y	0.57	.45	1
Last consumption (days)	23.1 (32.9), n=30	17.5 (32.9), n=29	0.43	.51	57
MDMA					
Status (y/n)[a]	0/56, 0.00% y	38/0, 100.0% y	94.0	**<.001**	1
Tablets per week[a,c]	0.00 (0.00)	0.90 (0.80)	-	-	-
Years of use	0.00 (0.00)	6.7 (6.1)	-	-	-
Cumulative dose (grams)	0.01 (0.04)	22.9 (27.7)	-6.2	**<.001**	92
Last consumption (days)	-	25.1 (20.9), n=38	-	-	-
Positive urine testing (y/n)[b]	0/56, 0.00% y	0/38, 0.00% y	-	-	-
Hair analysis pg/mg	0.00 (0.00)	4705 (8521)	-	-	-
Amphetamine					
Status (y/n)[a]	0/56, 0.00% y	22/16, 57.9% y	42.3	**<.001**	1
Grams per week[a]	0.00 (0.00)	0.03 (0.05)	-	-	-
Years of use	0.00 (0.00)	1.9 (2.9)	-	-	-
Last consumption (days)	-	29.7 (33.8), n=22	-	-	-
Cumulative dose (grams)	0.01 (0.03)	26.5 (107.3)	7.4	.07	92
Positive urine testing (y/n)[b]	0/56, 0.00% y	0/38, 0.00% y	-	-	-
Hair analysis pg/mg[e]	0.00 (0.00)	192.3 (689.5)	-	-	-
Cocaine					
Status (y/n)[a]	0/56, 0.00% y	20/18, 52,6% y	37.4	**<.001**	1
Grams per week[a]	0.00 (0.00)	0.11 (0.28)	-	-	-
Years of use	0.00 (0.00)	2.3 (3.6)	-	-	-
Last consumption (days)	-	29.3 (35.3), n=20	-	-	-
Cumulative dose (grams)	0.02 (0.05)	52.3 (150.6)	21.3	**.01**	92

Positive urine testing (y/n)[b]	0/55, 0.00% y	1/37, 0.03% y	1.5	.23	1
Hair analysis pg/mg	0.00 (0.00)	578.8 (1344)	-	-	-

Significant *p*-values are shown in bold. Statistical tests: independent t-tests for quantitative data, $\chi 2$ tests for frequency data.
BDI, Beck's Depression Inventory
Consumption per week, duration of use, and cumulative dose are averages within the total group.
Last consumption is an average only for persons who reported to have used the drug within the past 6 months. In this case, sample size (n) is shown. One urine sample (control), the ADHD-SR data for one participant (MDMA user), the years of scool education for one particant (MDMA user), and the duration of MDMA use for one participant were missing.
[a]During the past 6 months.
[b]For cut-offs, see the Supplementary Methods S1.
[c]In 100-mg tablets.

3.4.2 Social cognition

For cognitive empathy, two-way ANCOVAs revealed a significant main effect of group on the cognitive empathy domain score (CES) (*d*=.62) (Figure 1). Both measures constituting the CES also differed between groups – the MASC sum score (*d*=.50) and the MET sum score (*d*=.39) – indicating a better cognitive empathy performance of MDMA users compared to drug-naïve controls (Table 2). These group differences were driven by a superior emotion identification of the MDMA users for emotionally positively charged pictures in the MET (*d*=.47) and a reduced tendency to overmentalize (overinterpreted perspective-taking) in the MASC (*d*=.51). Neither for the MASC sum score, the cognitive empathy performance in the MET, nor the CES a significant group*sex interaction was found (Table 2).

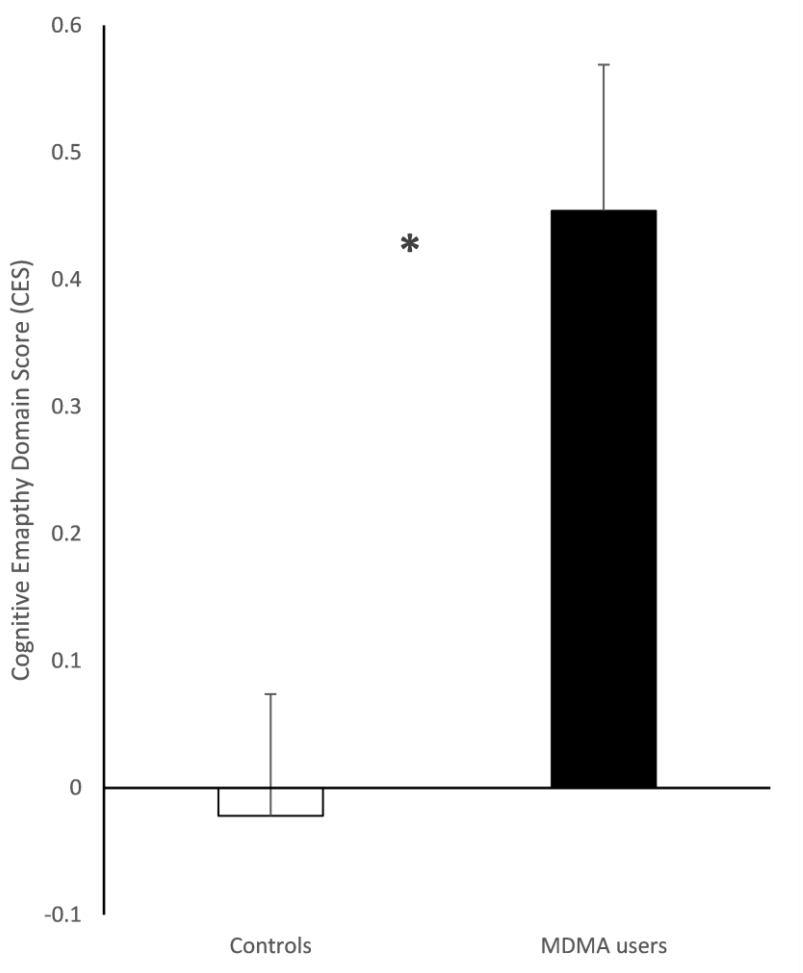
Regarding emotional empathy (MET), no significant group and group*sex interaction effects occurred (p>.24). However, the factor sex showed a significant impact. As expected, women showed higher emotional empathy ratings (*d*=.58) for positively (*d*=.43) as well as negatively charged pictures (*d*=.63) (Table 2, Figure 2).

TABLE 2: Emotional and cognitive empathy (means and standard errors)

	Controls	**MDMA users**	**F**	***df, df$_{err}$***	***P_group***	***p_IQ***	***p_sex***	***p_group_x_sex***
n	56	38						
MASC								
MASC sum correct[a]	34.8 (0.43)	36.4 (0.53)	6.0	1, 89	**.02**	.11	.81	.26
MASC sum no TOM	1.9 (0.23)	1.3 (0.28)	2.5	1, 89	.12	.34	.60	.33
MASC sum less TOM	3.3 (0.28)	3.4 (0.35)	0.03	1, 89	.87	.46	.30	.98
MASC sum too much TOM	5.1 (0.30)	3.9 (0.36)	6.2	1, 89	**.01**	.36	.08	.36
MET								
Emotional Empathy sum score (EES)	10.7 (0.31)	10.2 (0.37)	1.2	1, 88	.27	.93	**.006**	.35
EES over positive pictures	10.3 (0.37)	9.6 (0.45)	1.6	1, 88	.21	.44	**.04**	.24
EES over negative pictures	11.1 (0.31)	10.8 (0.37)	0.52	1, 88	.47	.46	**.003**	.65
Cognitive empathy sum score[a]	23.8 (0.48)	25.3 (0.57)	3.8	1, 88	**.05**	**.001**	.38	.52
CE over positive pictures	12.5 (0.31)	13.6 (0.37)	5.6	1, 88	**.02**	**.002**	.23	**.05**
CE over negative pictures	11.4 (0.36)	11.7 (0.43)	0.35	1, 88	.56	.09	.88	.39
Cognitive empathy domain score (CES)	-0.02 (0.10)	0.45 (0.12)	10.1	1, 88	**.002**	**<.001**	.48	.19

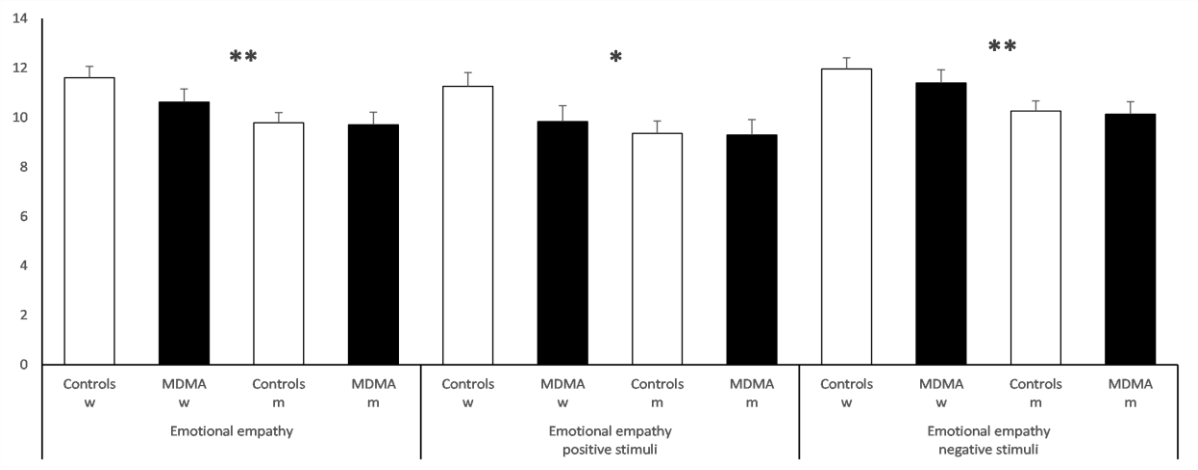
Significant *p*-values are shown in bold. Statistical test: Two-way ANCOVA with the factors group and sex and the covariate verbal IQ. CE, cognitive empathy, MASC, Movie for the assessement of social cognition, MET, Mulftifacetet empathy test,.
[a]Used for the cognitive empathy domain score.

Figure 1: Differences in a combined cognitive empathy score between controls (n=56) and MDMA users (n=37).



Estimated means and standard errors of the cognitive empathy domain score (CES). *p<.05.

Figure 2: Differences in emotional empathy between women (n=43) and men (n=50).

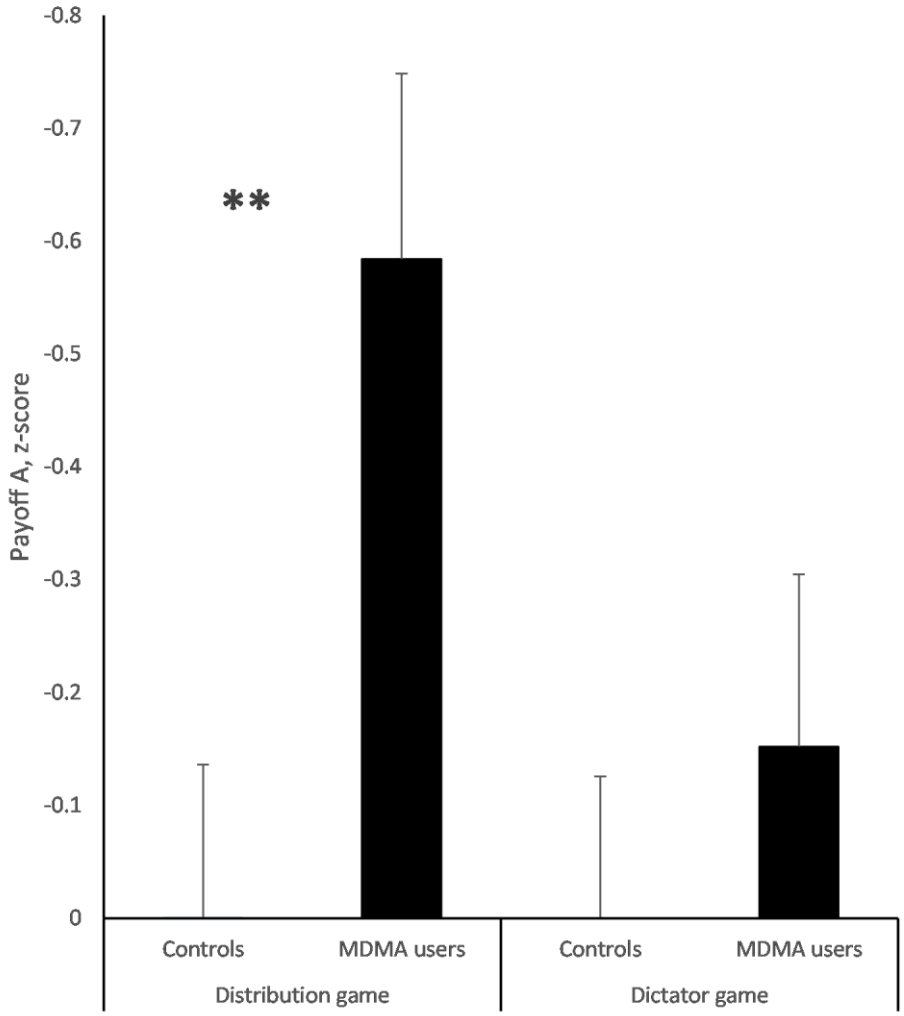


Estimated means and and standard errors of emotional empathy ratings for all emotionally charged pictures, emotionally positively charged pictures, and emotionally negatively charged pictures. *p<.05, **p<.01.

3.4.3 Social decision-making

Averaged across the Distribution Game and the Dictator Game, MDMA users (mean combined Payoff A=63.2±13.5 SD) exhibited less self-serving behavior than controls (67.9±14.0) as indicated by a significant difference in the combined score Payoff A ($F(1,90)=3.99$, $p<.05$, $d=.41$). The effect was mainly driven by the Distribution Game, in which MDMA users acted less self-serving ($d=.56$) (Figure 3). Accordingly, in this game, 53% of the MDMA users chose the only fair point distribution (50:50 for player A and B) as opposed to 25% of the controls ($\chi^2=7.50$, $p=.006$, $\varphi=.28$).

Figure 3: Differences in self-serving behaviour between controls (n=56) and MDMA users (n=38).



Estimated means and standard errors of the z-transformed payoff A (points participants gave to themselves) in the Distribution game and the Dictator game. **p<.01.

3.4.4 Clinical measures

MDMA users reported significantly more ADHD symptoms than controls (*d*=.66) (Table 3). In the BIS-11, the MDMA users displayed higher trait impulsivity (total score) compared with controls (*d*=.53). Likewise, significant main group effects were found for the subscales attentional impulsiveness (*d*=.41) and non-planning impulsiveness (*d*=.47). In the TCI, MDMA users differed from controls in novelty seeking (NS) scores (*d*=.57), driven by the sub-score disorderliness (NS4) (*d*=.52) (Table 3). Correlation analyses showed that severity of ADHD symptoms correlated significantly with BIS-11 attentional impulsiveness. Interestingly, TCI NS and NS4 scores neither correlated significantly with ADHD severity scores nor with BIS-11 scores (Supplementary Table S2).

TABLE 3: Clinical measures

	Controls	**MDMA**	***F***	***df, dferr***	***p***
n	56	38			
ADHD self-report rating scale (ADHD-SR)					
ADHD-SR sum score	7.7 (0.8)	12.0 (1.0)	10.7	1, 88	**.001**
Barratt Impulsiveness Scale (BIS-11)					
BIS-11 Total score	62.0 (1.2)	66.8 (1.4)	6.5	1,89	**.01**
FI Attentional impulsiveness	14.3 (0.4)	15.6 (0.5)	4.0	1,89	**.05**
FII Motor impulsiveness	21.9 (0.5)	23.2 (0.6)	2.9	1,89	.09
FIII Nonplanning impulsiveness	25.9 (0.6)	28.0 (0.7)	4.8	1,89	**.03**
Temperament and Character Inventory					
Self-directedness	33.8 (0.77)	32.4 (0.93)	1.4	1, 88	.24
Cooperativeness	33.5 (0.69)	32.2 (0.83)	1.4	1, 88	.23
Self-transcendence	10.8 (0.82)	12.1 (0.98)	0.92	1, 88	.34
Harm avoidance	12.8 (0.76)	11.2 (0.91)	2.0	1, 88	.16
Reward dependence	17.1 (0.48)	15.9 (0.58)	2.6	1, 88	.11
Persistence	4.0 (0.28)	3.2 (0.33)	3.3	1, 88	.07
Novelty seeking total score (NS)	22.3 (0.69)	25.4 (0.83)	7.8	1, 88	**.007**
NS1 Exploratory excitability	7.8 (0.27)	8.5 (0.32)	2.6	1, 88	.11
NS2 Impulsiveness	4.4 (0.32)	5.3 (0.38)	2.7	1, 88	.11
NS3 Extravagance	5.7 (0.27)	6.3 (0.32)	1.7	1, 88	.20
NS4 Disorderliness	4.3 (0.25)	5.3 (0.3)	6.3	1, 88	**.01**

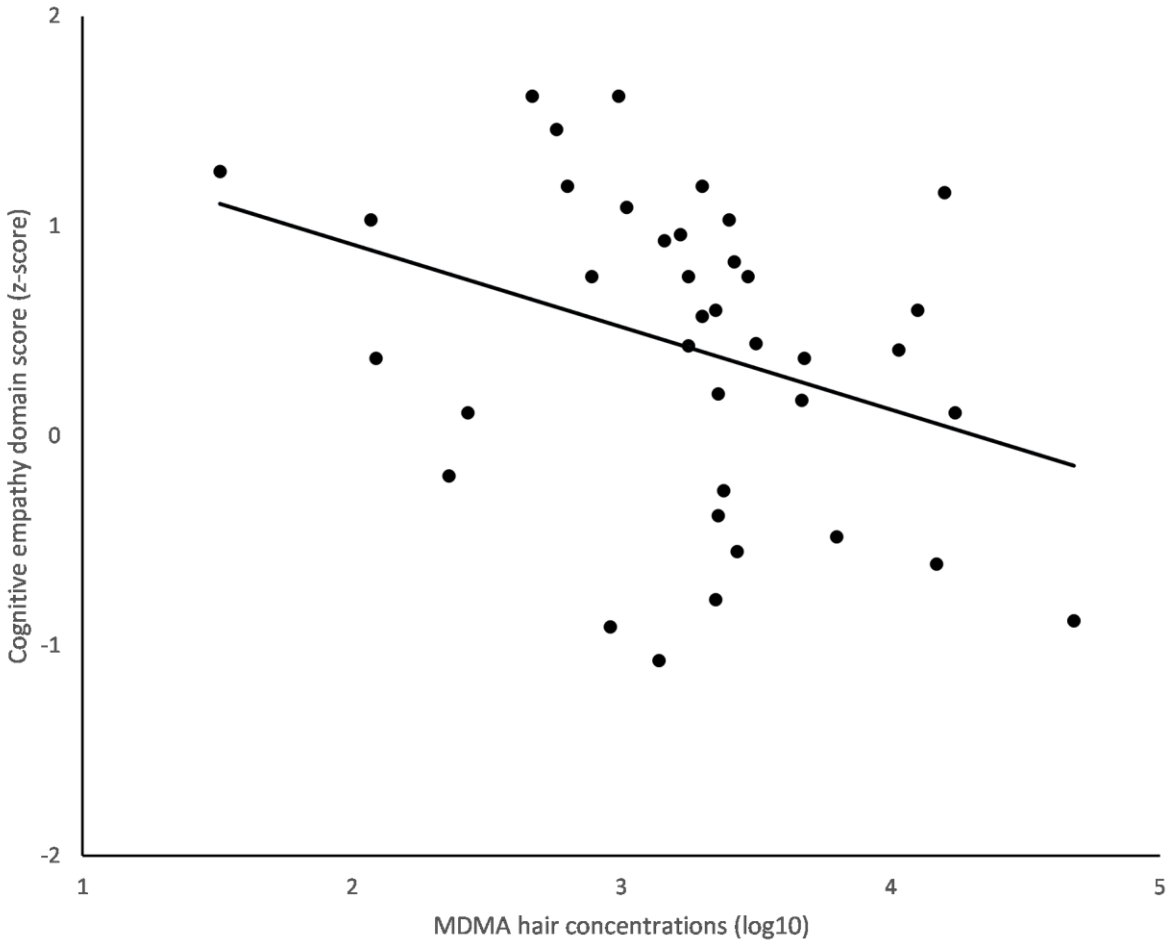
Estimated means and standard errors. Two-way ANCOVA (verbal IQ score as covariate, group and sex as factors). the ADHD-SR data for one participant (MDMA user) are missing. Significant p values are shown in bold.

3.4.5 Regression models

To analyze potential co-factors on cognitive empathy, we regressed the CES on demographic variables (age, sex, years of education, and verbal IQ). This analysis over all participants (n=94) revealed significance for the verbal IQ coefficient (β=.344, t=3.31, p<.001) only (Supplementary Table S3). In a second step, we additionally introduced a grouping variable (MDMA users vs. controls) into the model. This grouping variable significantly predicted cognitive empathy (β=.301, t=3.11, p<.01). The amount of explained variance (corrected) increased significantly (p<.01) from 9% in the model without the grouping variable to 17% in the model with the grouping variable (R^2_{corr}=0.17, $F_{5,87}$=4.70, *p*<.001).

Within MDMA users (n=38), again, verbal IQ was the only demographic variable significantly associated with cognitive empathy (β=.408, t=2.33, p<.05). To analyze the effect of MDMA on cognitive empathy, we therefore regressed the CES on the MDMA hair analysis and the verbal IQ score. Interestingly, of the two predictors, only higher MDMA hair concentration significantly predicted lower cognitive empathy (β=-.324, t=-2.13, p<.05) (Figure 4 and Supplementary Table S4). Consequently, we excluded verbal IQ in a second step. The change in F was non-significant (p=.09). In a third step, we added amphetamine and cocaine hair concentration values, self-reported lifetime cannabis consumption (in grams), as well as the duration of alcohol and nicotine consumption into the model. Because no objective measures were available for cannabis, alcohol and nicotine consumption, self-reported variables were used to operationalize the influence of these substances. Importantly, the amount of explained variance did not increase (p=.60) by adding these drugs into the model and none of the coefficients predicted cognitive empathy except for MDMA (p<.05). In conclusion, group differences in cognitive empathy cannot be explained e.g., by the co-use of stimulants of the MDMA users. Finally, MDMA hair concentration did neither predict emotional empathy nor prosocial behavior in MDMA users (β=.194, t=.947, p=.35 and β=.251, t=1.008, p=.32, respectively).

Figure 4: Regression of cognitive empathy on MDMA hair concentrations (pg/mg).

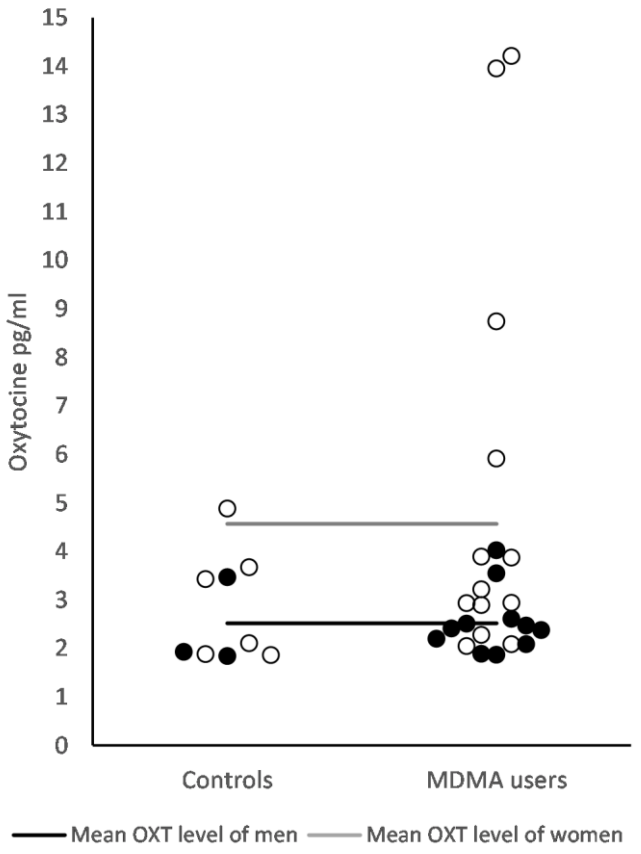


Regression of the CES z-score on the MDMA hair concentrations (log_{10}) of the MDMA users (n=38), $r(36) = -.34$, $p < .05$, two-way. Higher hair values were associated with lower cognitive empathy.

3.4.6 Oxytocin and empathy

Blood plasma OXT levels were available for 9 controls and 24 MDMA users only. A Mann-Whitney test indicated no group difference in blood plasma OXT levels between controls (median=13.56 pg/ml) and MDMA users (median=18.29 pg/ml), even though MDMA users unexpectedly showed moderately higher levels (U=139.0, p=.22, *d*=.42) (Figure 5). Within the MDMA users, blood plasma OXT levels did not correlate significantly with any MDMA use parameters. Moreover, women's OXT levels were ranked higher than men's were (r_s=-.35, p<.05). Finally, in accordance with the gender effects on both emotional empathy and OXT plasma concentrations, we found that higher OXT levels were positively correlated with higher emotional empathy (r_s=.44, p<.03) in MDMA users.

Figure 5: Mean peripheral blood plasma OXT levels (pg/ml) of controls (n=9) and MDMA users (n=24).



Groups did not differ signifianctly (p>.05, *d*=.42). Circles represent female and dots represent male participants.

3.5 Discussion

The aim of the study was to investigate empathy and social decision-making in objectively verified long-term MDMA users taking this drug as their main drug of choice. Detailed psychiatric diagnostics, hair toxicology, and matching were used to minimize the influence of psychiatric comorbidities and polydrug use. We showed that MDMA users display superior cognitive empathy compared with MDMA- and stimulant-naïve, healthy controls on one hand but that within MDMA users, increased MDMA hair contamination is associated with a decrease in cognitive empathy on the other hand. Additionally, MDMA users acted more pro-social than controls in the social decision-making tasks. Finally, the OXT system is likely not affected after long-term MDMA consumption, as peripheral OXY plasma levels were not significantly changed even though moderately elevated (d=0.42). In sum, these data suggest that recreational long-term MDMA users do not compensate for emotional empathy deficits by consuming MDMA (as no deficit was found), but rather show better cognitive empathy and pronounced prosocial behavior.

In line with previous studies investigating MDMA and stimulant users in general (Morgan, 1998; Butler and Montgomery, 2004; Vonmoos et al., 2014), our sample of main MDMA users showed increased trait impulsivity (BIS-11) together with higher novelty seeking scores (TCI) compared with drug-naïve controls. This characterizes our sample of MDMA users as a typical recreational drug user sample as proposed before (Rounsaville, 2004; Vonmoos et al., 2013a; Maier et al., 2015). However, our sample of MDMA users might be special given that it encompasses 26 relatively pure and stimulant-free MDMA users (Table 1). Thus, our findings of a superior cognitive empathy and prosocial behavior in MDMA users might be valid only for relatively pure MDMA users and not for the more typical type of polydrug MDMA users (Schifano et al., 1998). Moreover, cognitive empathy and prosocial behavior were not correlated with ADHD symptoms, impulsivity and novelty seeking (Supplementary Table S2). Thus, our finding of superior cognitive empathy and prosocial behavior cannot be explained by elevated impulsivity and novelty seeking in MDMA users. Interestingly, the higher cognitive empathy of the MDMA users in this study were mainly driven by a superior identification of positive emotions in the MET compared to controls. Therefore one might conclude that either 1) MDMA chronically induces a “positivity bias” with regard to cognitive empathy or 2) that people with a predisposed emotional “positivity bias” prefer MDMA as a recreational drug. In line with our findings, Hysek et al. (2012) showed that MDMA acutely enhances the ability to interpret stimuli with positive emotional valence correctly. Moreover, also the emotional empathy for positive stimuli is increased acutely (Hysek et al., 2014b). Thus, the valence of emotional stimuli is of critical importance when considering acute and chronic effects of MDMA on measures of empathy.

Using the same test battery, we have previously shown that relatively pure recreational and addicted cocaine users show impaired cognitive empathy (Hulka et al., 2013) and emotional empathy (Preller et al., 2014), which stands in strong contrast to the findings in MDMA users presented here. Hence,

although their personality traits (impulsivity and novelty seeking) resemble those of stimulant users, the group of relatively pure MDMA users seems to be a unique group of socially high performing drug users. This notion is further supported by our results regarding social decision-making as MDMA users, which, contrary to cocaine users (Hulka et al., 2014), acted more prosocial in the neuroeconomic games compared with controls. If this increased prosocial behavior of the MDMA users is a preexisting trait or rather a consequence of regular MDMA consumption cannot be explained by a cross-sectional study as the present one. Nevertheless, it seems plausible that repeated experiencing of interpersonal closeness leads to more prosocial behavior. Moreover, together with emotional empathy (empathic concern for others), cognitive empathy (mental and emotional perspective-taking) has previously been shown to correlate with affiliation motivation (Hill, 1987). More specifically, the underlying dimensions of *positive stimulation* – the tendency to receive gratification from harmonious relationships and from a sense of communion (Hill, 1987) – correlated highest with cognitive empathy. Thus, it seems likely that MDMA users display high affiliation motivation and that they use MDMA in social environments to satisfy this need for affiliation by MDMAs acute effect of enhanced emotional empathy (Hysek et al., 2014b).

The results of the regression analysis for demographic variables emphasize our finding of superior cognitive empathy in MDMA users in two ways: First, the group contrast remains significant, even when the variables age und years of school education are held constant in addition to verbal IQ and sex. Second, almost half of the explained variance in cognitive empathy is explained by the group contrast. Notably, within MDMA users, our regression model was most efficient when only the hair toxicology analysis of MDMA was entered into the model, indicating a possible detrimental chronic effect of MDMA on social cognition as it was predicted from animal studies before (Boot et al., 2000; McGregor et al., 2008; van Nieuwenhuijzen et al., 2010). We are aware that causal interpretations of drug effects derived from a cross-sectional investigation are speculative. Nevertheless, the present results are in line with earlier studies from our group showing dose dependent impairment of executive functions in MDMA users (Quednow et al., 2006; Quednow et al., 2007). In fact, cognitive empathy has been shown to correlate with executive functioning before (Eslinger et al., 2011) and in our sample, a domain-score of executive functions – according to Vonmoos et al. (2013b) and Wunderli et al. (2016) – was positively correlated with the MASC sum score ($r(92)=.227$, $p<.05$). Additionally, low recall consistency – as a measure for executive functioning – has been correlated with decreased glucose metabolism in the right dorsolateral prefrontal cortex in MDMA users in a recent PET study (Bosch et al., 2013). Given that adaptations in serotonin transporter density (McCann et al., 1998; Kish et al., 2010) as well as $5HT_{2A}$ receptor density (Reneman et al., 2002) in the prefrontal cortex have been reported in MDMA users, changes in the prefrontal 5HT system might be responsible for the demonstrated decrease in cognitive empathy that went along with increased MDMA hair concentrations. Finally, it would be interesting to investigate cognitive empathy in a MDMA user sample in a longitudinal study in which premorbid cognitive empathy scores are gathered and empathy

scores together with sustained drug use are measured over time in order to answer the question if the here shown changes are predisposed or MDMA-induced.

This study has some limitations. First, the common practice to measure drug use by means of self-reported drug assessments has been criticized before (Cole, 2014). Therefore, we objectively quantified our participants drug use via hair toxicology analyses but still had to rely on self-reports for alcohol, nicotine, and cannabis consumption. Being aware of this problem, we aimed to minimize the influence of these drugs by matching the groups accordingly. Second, we cannot rule out that the superior cognitive empathy of MDMA users is in fact a consequence at least of light or moderate MDMA consumption. Likewise, the implicated detrimental effect of MDMA on cognitive empathy is based only on the correlation between past drug use (hair analyses) across the last 3-6 months and current cognitive empathy. We therefore suggest that future research investigates this relationship in a longitudinal study. Third, our sample comprises 26 stimulant-free, pure MDMA users and might therefore not be generalizable to the prototypical recreational polydrug MDMA user. Fourth, our exploratory investigation of blood plasma OXT is based on a rather small sample size (n=24 users vs. n=9 controls). Moreover, peripheral OXT levels might not reflect the status of the neural OXY system (Kagerbauer et al., 2013). Therefore, the possibility of a long-term MDMA consumption effect on neural OXT systems still cannot be ruled out. We suggest that blood plasma OXT values of long-term MDMA users are compared to MDMA-naïve controls in a bigger sample in which sex is distributed evenly between groups. Moreover, an OXY receptor radioligand should be developed to investigate the status of the cerebral OXY system in human MDMA users by positron emission tomography.

Taken together, our data suggest that primary MDMA users show personality traits comparable to recreational stimulant users, but in contrast to those show superior cognitive empathy and more pro-social behavior than drug-naïve, healthy controls. Primary MDMA users might therefore be described as socially high performing drug users. However, because severe chronic MDMA consumption seems to have a toxic effect on cognitive empathy, we suggest that the superior cognitive empathy of MDMA users is not a consequence of MDMA use, but rather a predisposition for it. We conclude that main MDMA users do not consume MDMA to compensate for emotional empathy deficits, but are more prone to MDMA consumption because of pronounced cognitive empathy likely going along with high affiliation motivation.

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Conflict of Interest

All authors declare no competing interests and no potential conflict of interest with respect to the research, authorship, and publication of this article.

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3.7 Supplementary material

3.7.1 Methods

Methods S1: Urine and hair toxicology

Urine toxicology analyses comprised the following substances: tetrahydrocannabinol, cocaine, amphetamines, benzodiazepines, opioids, and methadone and were assessed by a semi-quantitative enzyme multiplied immunoassay method using a Dimension RXL Max (Siemens, Erlangen, Germany). For the detection of illegal drug use, the following cut-offs have been applied (Bush, 2008): Cannabis, 50 ng/ml; cocaine, 150 ng/ml; and amphetamines, 500 ng/ml.

To objectively characterize drug use over the last six months, hair samples were collected and analyzed with liquid chromatography-tandem mass spectrometry (LC-MS/MS). The proximal hair segment of a length of up to 6 cm was examined. The following 17 compounds were assessed: cocaine, benzoylecgonine, cocaethylene, norcocaine, amphetamine, methamphetamine, MDMA, MDEA, MDA, morphine, codeine, methadone, EDDP (primary methadone metabolite, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidene), tramadol, 2C-B, ketamine, and methylphenidate.

For our routine protocol for drugs of abuse analysis a three-step washing procedure with water (2 minutes shaking, 15ml), acetone (2min., 10ml) and finally hexane (2min., 10ml) of hair was performed. Then the hair samples were dried at ambient temperatures, cut into small snippets and extracted in two steps, first with methanol (5ml, 16 hours, ultrasonication) and a second step with 3 ml MeOH acidified with 50 µL hydrochloric acid 33 % (3 hours, ultrasonication). The extracts were dried and the residue reconstituted with 50 µL MeOH and 500 µL 0.2 mM ammonium formate (analytical grade) in water. As internal standards deuterated standards of the following compounds were used, added as mixture of the following compounds: cocaine-d3, benzoylecgonine-d3, ethylcocaine-d3, morphine-d3, MAM-d3, codeine-d3, dihydrocodeine-d3, amphetamine-d6, methamphetamine-d9, MDMA-d5. MDEA-d6, MDA-d5, methadone-d9, EDDP-d3, methylphenidate-d9, tramadol-d3, oxycodone-d3, and ephedrine-d3. All deuterated standards were from ReseaChem (Burgdorf, Switzerland), the solvents for washing and extraction were of analysis grade and obtained from Merck (Darmstadt, Germany); LC-solvents were of HPLC grade and were obtained from Sigma Aldrich (Buchs, Switzerland).

The LC-MS/MS apparatus was an ABSciex QTrap 3200 (Analyst software Version 1.5, Turbo V ion source operated in the ESI mode, gas 1, nitrogen (50 psi); gas 2, nitrogen (60 psi); ion spray voltage, 3500V; ion source temperature, 450°C; curtain gas, nitrogen (20 psi) collision gas, medium), with a Shimadzu Prominence LC-system (Shimadzu CBM 20 A controller, two Shimadzu LC 20 AD pumps including a degasser, a Shimadzu SIL 20 AC autosampler and a Shimadzu CTO 20 AC column oven, Shimadzu, Duisburg, Germany). Gradient elution was performed on a separation column (Synergi 4µ POLAR-RP 80A, 150x2.0 with a POLAR-RP 4x2.0 Security Guard Cartridge, (Phenomenex,

Aschaffenburg, Germany). The mobile phase consisted of 1mM ammonium formate buffer adjusted to pH 3,5 with formic acid (eluent A) and acetonitrile containing 1mM ammonium formate and 1 mM formic acid (eluent B). The analysis was performed in MRM mode with two transitions per analyte and one transition for each deuterated internal standard, respectively. According to the Society of Hair Testing (Society of Hair, 2004), the following cut-offs have been applied: cocaine, 500 pg/mg; amphetamine, 200 pg/mg; and MDMA, 200 pg/mg.

3.7.2 Results

Table S1. Hair analyses results (concentration values in pg/mg) of self-reported MDMA users and MDMA group allocation.

Subject	Hair sample taken?	MDMA group	MDMA	MDEA	MDA	Amphet-amine	Methamphet-amine	Cocaine	Methyl-phenidate	Morphine/ Codeine	Methadone/ EDDP	2C-B	Ketamine	Hair length[1]
1	yes	primary, pure	1985	0	55	0	0	445	0	0	0	0	n.a.	6
2	yes	primary, pure	975	0	30	55	0	45	0	0	0	n.a.	n.a.	6
3	yes	primary, pure	48000	40	150	60	0	80	0	0	0	0	n.a.	3.5
4	yes	primary, pure	1673	0	102	0	0	0	0	0	0	47	0	6
5	yes	primary, pure	915	0	45	59	0	156	0	0	0	0	0	2
6	yes	primary, pure	780	21	50	0	0	169	0	0	0	0	0	6
7	yes	primary, pure	4813	0	244	25	0	0	0	0	0	0	0	6
8	yes	primary, pure	2239	0	121	0	0	0	0	0	0	0	0	3.5
9	yes	primary, pure	2982	0	165	0	0	298	0	0	0	63	0	6
10	yes	primary, pure	1440	0	60	122	0	0	0	0	0	0	0	3.5
11	yes	primary, pure	626	0	41	0	0	0	0	0	0	0	0	6
12	yes	primary, pure	2408	114	117	160	0	0	0	0	0	0	0	6
13	yes	primary, pure	1763	0	125	15	0	0	0	0	0	0	0	6
14	yes	primary, pure	1054	0	60	191	0	78	0	0	0	0	250	6
15	yes	primary, pure	231	0	6	0	0	0	0	0	0	0	0	6
16	yes	primary, pure	1369	0	67	0	0	0	0	0	0	0	0	4
17	yes	primary, pure	2510	20	79	0	0	0	0	0	0	0	0	6
18	yes	primary, pure	267	0	9	0	0	0	0	0	0	0	0	6
19	yes	primary, pure	4670	0	331	0	0	81	0	0	0	0	0	6
20	yes	primary, pure	2695	0	182	0	0	0	0	0	0	0	0	6
21	yes	primary, pure	471	0	29	0	0	87	0	0	0	0	0	6
22	yes	primary, pure	2232	0	55	0	0	0	0	0	0	0	55	6
23	yes	primary, pure	32	0	5	0	0	0	0	0	0	0	0	6
24	yes	primary, pure	2625	0	119	195	0	0	0	0	0	0	0	6
25	yes	primary, pure	118	0	0	0	0	0	0	0	0	0	0	6
26	yes	primary, pure	123	0	9	0	0	219	0	0	0	0	0	6
27	yes	primary	17500	0	750	180	0	7700	0	0	0	n.a.	n.a.	6
28	yes	primary	10659	43	266	755	0	73	0	0	0	0	191	1.5
29	yes	primary	14863	31	317	0	0	2515	0	0	0	0	174	5
30	yes	primary	2298	54	117	93	0	713	0	0	0	0	0	6
31	yes	primary	12639	22	144	0	0	803	0	0	0	0	0	6
32	yes	primary	15731	29	1088	4228	0	1178	0	0	0	65	0	6
33	yes	primary	1778	0	116	540	0	1583	0	0	0	0	122	6
34	yes	primary	2000	0	30	140	0	1000	0	0	0	n.a.	n.a.	1.5
35	yes	primary	3150	0	215	105	730	590	0	0	0	n.a.	n.a.	6
36	yes	primary	6350	0	307.5	0	80	1750	0	0	0	n.a.	n.a.	6
37	yes	primary	570	0	48	210	0	480	10	0	0	n.a.	n.a.	2.5
38	yes	primary	2265	0	67.5	55	0	1950	89.5	0	0	n.a.	n.a.	4
39	yes	ex	754	0	50	0	0	**7233**	0	0	0	0	0	1.5
40	yes	ex	6050	0	303	**8324**	245	**4243**	0	0	0	0	31	6
41	yes	ex	134	0	0	**808**	0	88	0	0	0	56	0	6
42	yes	ex	146	0	0	**1013**	0	216	0	0	0	0	380	6
43	yes	ex	4650	0	195	**730**	0	**24500**	0	30	0	n.a.	n.a.	6
44	yes	ex	1200	0	20	0	0	**2000**	0	0	0	n.a.	n.a.	3
45	yes	ex	1150	0	100	**325**	0	**1275**	0	0	0	n.a.	n.a.	6
46	yes	ex	850	0	50	0	0	**2800**	0	0	0	n.a.	n.a.	6
47	yes	ex	835	0	15	0	0	**2900**	0	925	0	n.a.	n.a.	6
48	yes	ex	1000	0	35	0	0	**3300**	0	200	60	n.a.	n.a.	1.5
49	yes	ex	3750	145	150	**1850**	0	**15000**	0	0	0	n.a.	n.a.	6
50	yes	ex	10000	0	250	**440**	0	**10000**	0	0	0	n.a.	n.a.	1.5
51	yes	ex	2050	0	65	**230**	0	**3450**	0	0	0	n.a.	n.a.	6
52	no	ex	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	0	n.a.	n.a.	-
53	no	ex	n.a.	n.a.	n.a.	**n.a.**	n.a.	**n.a.**	n.a.	n.a.	0	n.a.	n.a.	-

For each participant, the amount of metabolites per substance (pg/mg) are shown. The cocaine metabolites benzoylecgonine, cocaethylene, and norcocaine are not shown. Tramadol is not shown because it was not detected in any subject. Strong stimulant co-consumption use leading to exclusion is shown in bold. To be included into the MDMA user group, hair samples had to reveal a larger MDMA concentration compared to cocaine and amphetamine values. To be classified as a pure MDMA user, hair samples had

to reveal a cocaine value <500pg/mg and an amphetamine value <200pg/mg (Cooper et al., 2012). Illicit drugs were not detected in the participants of the control group.

[1]Analyzed hair length from scalp in cm.

2C-B, 2,5-dimethoxy-4-bromphenethylamine; EDDP, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidene; ex, excluded; MDMA, 3,4-methylendioxy-N-methylamphetmanine; MDEA, 3,4-methylendioxy-N-ethylamphetmanine; MDA, 3,4-methylendioxyamphetamine; n.a., not available.

Table S2. Correlation analyses between clinical measures and social cognition in MDMA users (n=38).

	1	2	3	4	5	6	7	8	9	10	11	12
1) BIS-11 total score	1	.605***	.734***	.494**	.276	-.243	-.187	.117	-.075	.174	.314	.214
2) BIS-11 attentional impulsiveness		1	.118	.123	.114	-.059	-.031	.016	-.015	.149	.474**	.280
3) BIS-11 non-planning impulsiveness			1	.351	.071	-.200	-.298	.134	-.152	-.028	-.115	-.127
4) TCI novelty seeking				1	.694***	-.071	-.072	-.085	-.110	.191	.104	.094
5) TCI disorderliness					1	-.046	-.036	-.046	-.057	.332	.189	.140
6) MET emotional empathy						1	.136	-.448**	-.172	-.050	-.041	.057
7) MASC sum score							1	-.011	.783***	.043	-.027	.158
8) MET cognitive empathy sum score								1	.613***	.065	-.171	-.087
9) Cognitive empathy domain score									1	.075	-.132	.071
10) Self-serving behavior (Payoff A)										1	.154	.224
11) ADHS-SR sum score											1	.410
12) BDI sum score												1

Correlation coefficients are shown and p-values are indicated as follows: **p<.01, ***p<.001.
An ADHD-SR questionnaire of one participant was missing.

Table S3. Multiple Regression analysis for demographic variables predicting cognitive empathy (controls and MDMA users).

	B	SE *B*	β	T-value	*p*	$R^2_{corrected}$	p change in F
Step 1						*.086*	*.018*
Constant	-2.388	1.087		-2.198	**.03**		
Sex	-.137	.158	-.089	-.866	.39		
Age	-.023	.014	-.178	-1.652	.10		
Years of school education	-.014	.046	-.031	-.296	.77		
Verbal IQ	.033	.010	.344	3.310	**.001**		
Step 2						*.168*	*.003*
Constant	-9.623	2.547		-3.778	**<.001**		
Sex	-.121	.151	-.078	-.800	.43		
Age	-.021	.013	-.169	-1.639	.11		
Years of school education	.008	.045	.019	.185	.85		
Verbal IQ	.034	.009	.362	3.647	**<.001**		
MDMA users vs. controls	.470	.151	.301	3.110	**.003**		

Dependent variable: Cognitive empathy score (z-score). Significant *p*-values are shown in bold.
Step 1: R^2 = .13 and F = 3.152, p=.018.
Step 2: R^2 = .21 and F = 4.725, p<.001.
N = 94 (56 controls and 38 MDMA users).
The data met the assumption of independent errors (Durbin-Watson value = 2.16).
B = regression coefficient, SE *B* = standard error, β = standardized Beta.
Females were coded with 0 and males with 1 for the sex variable.
For the group comparison, controls were coded with 0 and MDMA users with 1.

Table S4: Multiple Regression analysis for drug use variables predicting cognitive empathy (only MDMA users).

	B	*SE B*	*β*	T-value	*p*	$R^2_{corrected}$	p change in F
Step 1						*.143*	***.025***
Constant	-.861	1.556		-.553	.584		
Verbal IQ	.024	.014	.271	1.775	.085		
MDMA hair concentration (pg/mg)	-.374	.176	-.324	-2.128	**.040**		
Step 2						*.092*	*.085*
Constant	1.701	.600		2.836	**.007**		
MDMA hair concentration (pg/mg)	-.393	.181	-.341	-2.177	**.036**		
Step 3						*.058*	*.600*
Constant	1.965	.717		2.742	**.010**		
MDMA hair concentration (pg/mg)	-.575	.222	-.499	-2.589	**.015**		
Amphetamine hair concentration (pg/mg)	.190	.113	.292	1.683	.102		
Cocaine hair concentration (pg/mg)	.036	.103	.066	.347	.731		
Cannabis lifetime dose (g)	-.029	.106	-.046	-.273	.786		
Alcohol (years of use)	.066	.346	.033	.191	.850		
Nicotine (years of use)	.134	.302	.078	.445	.659		

Dependent variable: Cognitive empathy score (z-score). Significant *p*-values are shown in bold.
Step 2: R^2 = .12 and F = 4.739, p=.036.
N = 38 primary MDMA users.
The data met the assumption of independent errors (Durbin-Watson value = 2.34).
B = regression coefficient, SE *B* = standard error, β = standardized Beta, g/week = grams per week, pg/mg = picogram per milligram.
All predictors (except for verbal IQ) were log-transformed (base 10).

3.7.3 References

Bush DM (2008) The U.S. Mandatory Guidelines for Federal Workplace Drug Testing Programs: current status and future considerations. Forensic Sci Int 174:111-119.

Cooper GA, Kronstrand R, Kintz P, Society of Hair T (2012) Society of Hair Testing guidelines for drug testing in hair. Forensic Sci Int 218:20-24.

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4 General Discussion

This doctoral thesis investigated chronic effects of MDMA use on social and non-social cognitive performance by comparing relatively pure users of MDMA with MDMA- and stimulant-naïve controls. In the first study, we investigated the detrimental effects of stimulant co-use by including a third group of MDMA polydrug users mainly co-using MDMA with stimulants such as amphetamines and cocaine. A special feature of both investigations is the objective measurement and description of the participants drug use by quantitative hair analyses. Because of these measures, we were able to distinguish between probably stimulant induced impairments regarding cognitive performance in the first study and to statistically rule out polydrug use as an explaining factor in the second study.
In what fallows, the main findings of the two papers together with their strengths and limitations will be briefly summarized. The first study investigated attention, working memory, declarative memory and executive functions in relatively pure MDMA users in contrast to MDMA- and stimulant-naïve controls as well as polydrug MDMA users. The second study investigated social cognition and decision making in main MDMA users in contrast to MDMA- and drug-naïve controls.

4.1 Cognitive performance of pure vs. polydrug MDMA users

The results of the first study are in line with previous meta-analyses (Kalechstein et al., 2007; Laws and Kokkalis, 2007; Rogers et al., 2009) and confirmed our hypothesis that the strongest impairments in pure as well as polydrug MDMA users are found in declarative memory performance. Additionally, they show that even in almost pure MDMA users considerably large declarative memory deficits occur. In all four cognitive domains, effect sizes of cognitive impairment of pure MDMA users were between controls' and polydrug MDMA users', whereby – besides declarative memory – also working memory performance differed significantly from controls. This is in line with Rogers et al. (2009), as verbal declarative memory and working memory were the two most impaired cognitive functions in MDMA users in their meta-analysis too. By the means of regression analyses, we investigated potential co-factors and dose-response effects on declarative memory performance. This analysis over all participants strengthened our finding as group contrasts remained significant even when sex, age, and verbal IQ were held constant. These three variables are of special interest in the context of long-term deficits in MDMA users. 1) Women were shown to be more susceptible to MDMA-induced neurotoxic effects (SERT reduction) (Reneman et al., 2001) than males. 2) Age is associated with a decline in cognitive processes, specifically in attention and memory tasks (Allott and Redman, 2007) while 3) verbal IQ is a correlate of global cognitive abilities. Similarly, also ADHD and depression scores did not significantly contribute to the regression model, while group contrasts remained significant. This was surprising as we have shown an association between ADHD as well as depression scores and cognitive difficulties in cocaine users before (Vonmoos et al., 2013b; Wunderli et al., 2016) and was probably due to our exact matching procedure which lead a reduced variance in

depression and ADHD scores. Additionally, it is also possible that – in contrast to cocaine – MDMA does not interact with depression or ADHD scores.

Interestingly, neither MDMA hair concentrations nor the MDMA lifetime dose predicted memory performance significantly. Although some studies have found correlations between lifetime MDMA consumption and cognitive deficits (Gouzoulis-Mayfrank et al., 2000; Quednow et al., 2006), this non-finding is in line with the theory of a stepwise relationship between MDMA use and memory decline (Laws and Kokkalis, 2007). According to this idea, a one-off recreational dose may be responsible for a negative effect and later recreational consumption does no further harm (Verbaten, 2003; Laws and Kokkalis, 2007). Finally, we showed that within MDMA users, the lifetime consumption of cannabis was significantly associated with a decline in declarative memory (besides the group contrast). This is in line with a large body of literature connecting cannabis use with cognitive impairments (Curran et al., 2016) and shows, that in drug research, cannabis consumption must be considered when interpreting results.

In sum, these results indicate a strong risk for broad cognitive impairments in polydrug MDMA users and show that even relatively pure MDM A users show robust impairments in declarative memory. Finally, the strong working memory and executive function impairments in polydrug MDMA users seem to be driven by their stimulant co-use.

4.2 Social cognition and decision making of main MDMA users

The second study confirmed previous findings investigating MDMA and stimulant users (Morgan, 1998; Butler and Montgomery, 2004; Ersche et al., 2011; Vonmoos et al., 2014) in as far as our MDMA users displayed elevated measures of impulsivity and novelty seeking compared with controls. Therefore, our sample of main MDMA users shows trait measures that are considered typical for recreational drug user samples (Rounsaville, 2004; Vonmoos et al., 2013a; Maier et al., 2015). This is of interest because our finding of a superior cognitive empathy of main MDMA users compared with controls might else be rejected with the argument of an over performing sample which is well educated, intellectual, and cognitively high performing. To examine cognitive empathy, we correlated cognitive empathy performance with a variety of clinical measures including ADHD and depression scores. None of these correlations were significant. This further supports our finding of an increased cognitive empathy in main MDMA users as group differences are not attributable to differences in clinical measures. This therefore additionally strengthens the association between our MDMA user sample and it's increased cognitive empathy on the one hand. On the other hand, also our finding of a decline in cognitive empathy that goes along with increased MDMA hair values is supported, as this decrease cannot be attributed to ADHD and depression scores within MDMA users.

In addition to an increased cognitive empathy, our sample of main MDMA users also displayed less self-serving behavior in our task of social decision making. This finding was in contrast to Hulka et al. (2014) who reported decreased prosocial behavior in a cocaine user sample. However, the increased

prosocial behavior of our main MDMA users in comparison to the control group together with their cognitive empathy abilities suggests, that MDMA user with little to none stimulant co-use can be described as socially high performing drug users. Interestingly though, the MDMA users did not differ from controls in emotional empathy measures, which is what we would have expected given the functual linkage between emotional empathy and OXT (Thompson et al., 2007; Kirkpatrick et al., 2014).

Our findings regarding OXT levels in MDMA users in comparison to controls did not support findings of OXT depletion after repeated MDMA administration coming from animal studies (van Nieuwenhuijzen et al., 2010). Indeed, our MDMA sample even showed slightly higher OXT blood plasma levels. However, this difference did not reach significance probably due to the low power of this comparison. However, according to existing literature that reported higher emotional empathy and higher OXT levels in women (Fukushima and Hiraki, 2006; Rueckert and Naybar, 2008), we found that higher OXT levels did positively correlate with higher emotional empathy. This strengthens the validity of our OXT measures and therefore these findings could motivate future research to investigate the possible elevation of OXT levels in MDMA users.

4.3 Strengths

The design of the studies constituting this thesis has a number of strengths worth mentioning.

First, the use of urine and hair analyses enabled us to monitor recent polydrug as well as past drug use over the past six month respectively. Urine toxicology analyses are considered to be accurate in detecting recent cocaine and amphetamine consumption (Moeller et al., 2008), the most co-used drugs in our sample. As urine toxicology analyses in our studies were performed by semi-quantitative enzyme multiplied immunoassays, it must be noted that results are presumptive only, although using urine analyses is considered common practice in drug research nowadays (Moeller et al., 2008). Thus, we did not exclude urine positive participants because of power considerations, according to other publications from the ZuCo^{2}St (Vonmoos et al., 2013b; Hulka et al., 2014; Preller et al., 2014). Unfortunately, our urine analyses did not screen for MDMA, as amphetamine immunoassays show a low sensitivity for the detection of MDMA (Hsu et al., 2003; Moeller et al., 2008). We therefore relied on the hair toxicology analyses. This enabled us to quantify objectively the participants' drug use for up to six month. Accordingly, we excluded two participants from the analyses because of a lack of hair and additional 13 participants in study 2, as their stimulant co-consumption exceeded their MDMA use.

Second, trained psychologists conducted the SCID I in order to exclude participants with a severe Axis-I disorder. In addition, participants were also excluded if close relatives were diagnosed with these disorders because of possible genetic components (schizophrenia, obsessive-cumpulsive disorder, eating disorder, etc.).

Third, subclinical levels of ADHD and depression were considered in both studies in the regression models in order to evaluate their impact on declarative memory and cognitive empathy, as both ADHD and depression are associated with drug abuse in general (Swendsen and Merikangas, 2000; Regnart et al., 2017).

Fourth, we assessed the personality structure of our sample by applying the BIS-11 and the TCI (reported in study 2). We therefore were able to characterize our sample even more precisely and show that our sample of MDMA users resembles typical recreational drug users.

Fifth, although our samples were not huge, they can be considered large in comparison to other cross-sectional studies investigating MDMA user. Consequently, main effects in both studies had an alpha-error probability of 5% and a power of 85% and 80% respectively.

Fifth, evidence for MDMA induced cognitive impairments accumulated in the past 30 to 40 years (Kelly, 2000; Parrott, 2014). The results of our first study are in line with these findings and extend the existing literature by eliminating the often-applied criticism of self-reported drug use. Regarding social-cognition, our second study showed increased cognitive empathy and prosocial behavior in main MDMA users, but also a decline in cognitive empathy with increased MDMA hair values. We therefore propose that an increased cognitive empathy and prosocial behavior are predisposing traits of

people especially prone for long-term MDMA consumption and deliver evidence for a possible detrimental effect of MDMA use on social cognition for the first time.

4.4 Limitations

Besides the outlined strengths of our studies mentioned before, there are some limitations to consider. Although urine toxicology analyses were used to verify the absence of recent drug use such as amphetamine, cocaine, benzodiazepines, cannabis, methadone, and opioids, we had to rely on participants' self-reported abstinence duration for MDMA use. Additionally, we had to rely on self-reports for the consumption parameters of alcohol, nicotine, and cannabis, but we minimized the influences of these variables by matching. A further limitation that should be mentioned is that also pure and main MDMA users consumed alcohol, nicotine, and cannabis. We tried to control the effects of these substances by matching the groups accordingly, but we remain unaware of possible interaction effects between MDMA and these substances.

Besides the limitations already mentioned in study one and two, some test specific weaknesses of the applied tasks in the two studies that deserve mentioning. In the first study, we operationalized declarative memory by combining variables from the RAVLT and the PAL according to previous publications from the ZuCo^{2}St (Vonmoos et al., 2013b; Wunderli et al., 2016). Although verbal (RAVLT variables) as well as visual (PAL) aspects of declarative memory are measured with these variables, they measure the retrieval of memories that have been stored for a maximum of around 30 minutes only. In the second study, the domain of cognitive empathy consisted of the MASC sum score and the cognitive empathy sum score from the MET. For the MASC, Dziobek et al. (2006) noted that all of the actors in the movie have roughly the same (mid-thirties). Because our participants had an average age of around 26 years and the age of the actors serves as the context in which social cognition has to be assessed in MASC, one might argue that scenes with actors with a wider age range would be more optimal. Another downside of the MASC might be that the movie is rather uninteresting to watch and that the task takes around 30 minutes to complete. Attentional as well as motivational differences between participants might therefore influence their performance.

Finally, a cross-sectional study does not allow causal conclusions about the direction of the relation between to associated variables. In the context of our studies, this means that MDMA cannot be labeled the cause of declarative memory deficits and a decline of cognitive empathy. Nevertheless, our results strongly imply this relationship in the context of the large body of literature including longitudinal investigations in humans (e.g. Wagner et al., 2015), already pointing in this direction.

4.5 Implications and Perspectives

The main aim of this behavioral research in MDMA users is to extend the knowledge on the relation between MDMA use and social and non-social cognitive processes. Particularly because an increase in worldwide MDMA consumption has been observed in recent years (United Nations Office on Drugs and Crime, 2016, 2017) there is the need to better understand consequences of long-term MDMA use in order to better estimate possible detrimental chronic effects of this substance. Although cognitive consequences of MDMA use were already well-documented in MDMA users (Fox et al., 2001; Montgomery et al., 2005; Quednow et al., 2006; Quednow et al., 2007) and a number of reviews have been published on the topic (Parrott, 2001; Laws and Kokkalis, 2007; Rogers et al., 2009; Parrott, 2013), our research extended the knowledge about consequences of MDMA use by eliminating the confounding effects of stimulant co-use and by investigating social cognition and decision making in an objectively verified main MDMA user sample for the first time. Although the presented studies do not conclude concrete instructions about how to translate the finding into a clinical setting, they clearly imply how future behavioral MDMA research (and drug research in general) could and should be improved.

First, results from the first study show that concurrent or even contemporary consumption of MDMA and stimulants should be avoided, because of stronger cognitive impairments in polydrug MDMA users in comparison to relatively pure MDMA users. This is line with animal studies showing that the combined administration of MDMA and prodopaminergic agents leads to a potentiation of serotonergic neurotoxic effects of MDMA (Johnson et al., 1991; Johnson and Nichols, 1991; Schmidt et al., 1991; Clemens et al., 2005) and is of concern in the context of the repeatedly shown variability in the purity of MDMA tablets (Morgan, 1999; Parrott, 2004). For future research, our finding of stronger cognitive impairments in polydrug MDMA users therefore implies the need for objective drug use and group assessments. In addition to stimulant co-use, the need for a reliable assessment of cannabis consumption is implicated by the results of our first study too. This need is underlined by the fact that MDMA users often co-use cannabis on a regular basis (Parrott et al., 2007). However, it was not possible to determine THC-metabolites in hair in our study.

Second, our second study on social cognitive functioning indicates that main MDMA users with little to none stimulant co-use can be considered socially high-performing, while they yet display trait impulsivity and novelty seeking measures comparable to recreational stimulant users. Because an increased impulsivity is linked to a higher risk of stimulant abuse (Verdejo-Garcia et al., 2008; de Wit, 2009; Ersche et al., 2010; Vonmoos et al., 2013a), our data suggest that long-term pure MDMA consumers could be a reasonable target of drug abuse prevention programs with the aim to prevent them from engaging in regular stimulant use.

Third, the ZuCo^{2}St revealed that social and non-social cognition are strongly moderated by comorbid ADHD symptoms in cocaine users (Vonmoos et al., 2013b; Preller et al., 2014) and we recently

reported detrimental interaction effects between cocaine use and ADHD on cognitive empathy/ToM (as measured by the MASC) (Wunderli et al., 2016). We did not find this moderating effect of ADHD on cognition nor social cognition in the two studies presented in this thesis. This may be due to the overlap of the brain systems altered in ADHD with the dopaminergic, cocaine-impacted neurotransmitter systems that differs from the serotonergic system impacted by MDMA and also play a crucial role in the etiology of ADHD (Tripp and Wickens, 2009).

Fourth, regarding the differences in peripheral OXT levels in MDMA users discussed before, we propose that future research investigates the impact of chronic MDMA consumption on neural OXT levels. By developing a radioligand to measure OXT receptor density in humans by positron emission tomography, future research could answer the question if chronic MDMA use alters the neural OXT system but also, if peripheral OXT levels really mirror the neural ones, which was critically discussed before (Kagerbauer et al., 2013) .

Fifth, our main MDMA user sample in study 2 included 26 non-stimulant using MDMA users. Because therefore our results may not be generalizable to typical (polydrug using) MDMA users (Schifano et al., 1998), social cognition and decision making should be investigated in a more typical MDMA user sample in the future.

Sixth, the amount of self-reported MDMA use fluctuates between studies because 1) participants might be motivated to give a biased self-report and 2) because participants might over- or underestimate their own drug use. Additionally, regional differences in drug availability and drug use culture may also induce differences in drug use samples across studies. For example, Quednow et al. (2006) investigated MDMA users with a mean cumulative lifetime dose of 460 tables, Montgomery et al. (2005) investigated a sample reporting a mean lifetime consumption of 346 tablets, and the main MDMA users of our second study reported a mean MDMA lifetime dose of 229 tablets. As we were able to find significant regression coefficients for MDMA hair values, which only capture the past half year, already, one has to be aware of these differences when interpreting results.

Seventh, finally, it would be interesting to investigate cognition and non-social cognition in an objectively verified MDMA user sample in a longitudinal setting. By measuring premorbid cognitive and social cognitive performance and by repeated collection of hair samples, a continuous tracking of the drug intake of every participant would be possible. For the issue that human participants cannot be asked to engage in chronic MDMA use for the sake of a longitudinal investigation, a compelling solution was found by Wagner et al. (2015). The authors included inexperienced MDMA users (less than 6 tablets) with a high probability of future MDMA consumption into their longitudinal analysis. Such a design (together with a non-MDMA and non-drug using control group) would allow for causal conclusions about the relationship between chronic MDMA use and social and non-social cognitive impairments.

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